Dear Editor,

We submit a revised version of our invited editorial titled "Novel insights in the prevention of perinatal transmission of hepatitis B" for consideration for publication in the World Journal of Hepatology. We thank the Reviewers for their comments, which improved our paper. We modified the text according to these comments. All changes are shown in red in the revised text.

Response to Reviewers' comments

Reviewer's code: 02530754

The manuscript by K. Tziomalos and cols. is an interesting editorial regarding strategies to prevent perinatal transmission of hepatitis B. The topic is of high relevance and the manuscript is informative and well written.

We thank this Reviewer for these positive comments.

The authors are kindly invited to consider the following comments:

- The authors stated that: "Lamivudine, telbivudine and tenofovir also appear to be safe during pregnancy and do not increase the risk of congenital malformation, prematurity or maternal complications". Consider including FDA pregnancy category for the above referred antivirals. I am aware that this information can be read later on in the manuscript but I believe it is important to refer it earlier. Most importantly, telbivudine and tenofovir are both considered as class B and not only tenofovir. Please amend accordingly.

We thank this Reviewer for this important comment. We added at this point "However, it should be emphasized that tenofovir and telbivudine are both FDA pregnancy category B drugs (i.e. no risk in animal studies, unknown in humans) whereas lamivudine is FDA pregnancy category C drug (i.e. teratogenic in animal studies, unknown in humans)".

- Immediately thereafter it can be read: "combining a nucleoside analogue with HBV immunoglobulin/HBV vaccination is more cost-effective than HBV immunoglobulin/HBV vaccination alone". In what context? Cost effectiveness studies are applicable only to the population they are derived from. Please comment.

We thank this Reviewer for this insightful comment. We changed this phrase to "It has also been shown that in the United States, a country with very low prevalence of CHB, combining a nucleoside analogue with HBV immunoglobulin/HBV vaccination is more cost-effective than HBV immunoglobulin/HBV vaccination alone".

- Any recommendation regarding breast feeding?

We thank this Reviewer for this constructive comment. We added in page 6 "Regarding breastfeeding, current guidelines state that it is not contraindicated in HBsAg(+) women who are not receiving nucleoside analogues, since breast milk contains the lowest concentrations of HBV among body fluids and breast feeding does not increase the risk of HBV transmission in women who receive HBV immunoglobulin and HBV vaccination. Moreover, breastfeeding is also not prohibited in women who are receiving prophylaxis with tenofovir, since this agent is excreted in very small amounts in breast milk."

- In the conclusion the authors wrote: "However, even in high-income countries, less than half of HBsAg-positive pregnant women are identified and appropriately managed for prevention of perinatal HBV transmission". This statement is supported by a single reference based on fairly old data (more than 10 years ago; ie. 1999-2008). I am not convinced that this is the current scenario in developed countries (even in the quoted paper the situation improved over the evaluated period). I agree with the authors that continued awareness of this problem is certainly warranted but this statement

should be either supported by more recent studies or rephrased to mirror the current situation.

We agree with this comment and we removed this sentence. We also mention in the last phrase of the conclusions "Strategies to improve the awareness of this major healthcare problem are also needed to curb the rising incidence of CHB infection."

- The authors recommended that antiviral prophylaxis with tenofovir may be useful in women with high viral loads. An approximate threshold would be welcomed. In recent clinical guidelines a threshold of serum HBV DNA >200.000 IU/m has been proposed.

We mention in page 6 "In all pregnant women with HBV DNA levels > 200,000 IU/ml and/or > 6-7 log_{10} IU/ml or HBsAg levels > 4 log_{10} IU/ml, antiviral prophylaxis with tenofovir should start at week 24-32 of gestation and continue for up to 4-12 weeks after delivery [25-27]."

Reviewer's code: 02942798

Dear Sir, thank you to select me to review an editorial: Tziomalos K et al. Novel insights in the prevention of perinatal transmission of hepatitis B. Topic is interesting, editorial is wel written.

We thank this Reviewer for these positive comments.

Only minor changes are recommended: 1) High chronic HBV infection prevalence, poor compliance with medical care and barriers to health care among low-income population groups, especially in immigrants and Roma population, are associated with increased perinatal hepatitis B transmission even in developed European countries (Papaevangelou V, et al. BMC Infect Dis. 2006 May 9;6:84. Drazilova, S et al. Int J Environ Res Public Health. 2018;15(5). pii: E1047. doi: 10.3390/ijerph15051047.)

We added in page 4 "High chronic HBV infection prevalence, poor compliance with medical care and barriers to health care among low-

income population groups, especially in immigrants and Roma population, are associated with increased perinatal hepatitis B transmission even in developed European countries" and we cite these interesting papers.

2) Discuss in 2 or 3 sentences the role of caesarean section to prevent perinatal HBV transmission (Chang MS et al. Can J Gastroenterol Hepatol. 2014 Sep;28(8):439-44.)

We added in page 6 "The role of caesarean section in the prevention of perinatal transmission of HBV infection is unclear. In a recent meta-analysis of 10 studies (n = 5,091 newborns), caesarean section reduced the incidence HBV transmission by 38% compared with vaginal delivery (95% confidence interval 0.40-0.98, p=0.04). However, the benefit of caesarean section was smaller in studies where HBIG was administered to all women. Moreover, caesarean section did not reduce the risk of vertical HBV transmission in HBeAg(+) women. Accordingly, current guidelines do not recommend caesarean section for the prevention of perinatal transmission of HBV infection due to insufficient data." and we cite this important meta-analysis.

3) Please replace category B, category C with FDA pregnancy category B, FDA pregnancy category C (page 5).

We made this change.

We look forward to your decision.

Best regards,

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