Reviewer's code: 00052926

This is a very interesting study on the safety of telbivudine administration in pregnancy and its efficacy in preventing mother-to-child-transmission of HBV infection. The data are well analysed and written and the conclusions are useful particularly for the HBeAg positive mothers with high viral loads.

Comments:

1. Please determine the maternal HBV DNA in the publications stated in the article if it is possible and add them in Table 3. (Range, median or mean value).

   Response: Thank you for your review comment. We have added the maternal HBV DNA information as per the source papers in Table 3. Of the 18 publications, 16 papers had provided inclusion criteria of HBV DNA prior to telbivudine treatment; 2 papers did not provide HBV DNA data prior to telbivudine treatment.

2. What was the maternal HBV DNA in the cases who had vertical transmission of HBV infection despite telbivudine prophylaxis? When the mothers did start telbivudine in these cases (1st, 2nd or 3rd trimester)?

Response: Thank you for your review comment. As reported from 9 papers, there were 11 infants who had vertical transmission of HBV infection and were born to telbivudine treated mothers during pregnancy. Of the 11 cases, 6 mothers had > 6 log copies/mL HBV DNA prior to telbivudine treatment, 2 mothers had > 5 log copies/mL and 2 mothers had > 3 log copies/mL. HBV DNA level was not reported in 1 mother. Of the 11 infants, 8 mothers started telbivudine treatment from 3rd trimester and 3 mothers started from 1st trimester. Relevant information has been added to the "Results" section of the manuscript.

3. From the analysis of trials birth defects in telbivudine cases were not more prevalent than usual. However, in the registry, only 27 cases with telbivudine prophylaxis were reported. Is it safe to draw conclusions from this small number of cases?

Response: Thank you for your review comment. The APR registry data is only a reference database in our study. The conclusion of our study is not drawn from the APR data, but based on the 18 literature studies. Our conclusion is based on 1725 mothers treated with telbivudine during pregnancy and we believe this is a solid evidence based conclusion.

4. What the authors believe about the start of antiviral treatment? Is it safe and necessary to start at the 1st, 2nd or 3rd trimester? What do they recommend about the administration of treatment according to maternal viral load? All women with HBV DNA > 106-7 should take antivirals? Please comment both on safety and efficacy of the regimens.

Response: According to EASL CHB guidelines, "Mothers with these high concentrations of HBV DNA should be informed that utilizing a NA to reduce their viral loads could add to the effectiveness of HBIg and vaccination (B1). Lamivudine and recently telbivudine therapy during the last trimester

of pregnancy in pregnant HBsAg-positive women with high levels of viremia have been shown to be safe and to reduce the risk of intra-uterine and perinatal transmission of HBV if given in addition to passive and active vaccination by HBIg and HBV vaccination (B1). Thus, telbivudine, lamivudine or tenofovir (as a potent FDA category B agent) may be used for the prevention of perinatal and intra-uterine HBV transmission in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA >10^{6-7} IU/ml) (B1)."

Based on the analysis of our study, telbivudine usage in pregnant women in all pregnancy trimesters is generally safe and efficacious. Our study results are in accordance with EASL guidelines. Moreover, at least 297 mothers with telbivudine exposure during 1st trimester were included in our study. Of note, 4/6 infants with birth defects were born to mothers who were exposed to telbivudine in the 1st trimester; and 8/11 infants with MTCT were born to mothers who were exposed to telbivudine in the 3rd trimester of pregnancy. Accordingly, the starting trimester of telbivudine treatment should be a balanced decision considering the maternal HBV DNA load and the need of minimizing risk of birth defects to achieve a best efficacy and safety outcome. Relevant discussion points have been added to the "Discussion" section of the manuscript.

5. In the section "Characteristics of the selected cases" the authors report 18 publications and state Table 3. However, Table 3 includes 21 publications, 4 of them being case reports with only 1, 1, 5, 5 individuals. Please make corrections if it is needed

Response: Thank you for your review comment. In the previous version, some publications appeared in 2 lines. There are 18 publications included in this study. One paper is a single case report; and another paper is a case series of 5 cases. Table 3 has been reformatted to make it easier for understanding.

Reviewer's code: 00052899

In the review, the authors summarized the information of women with HBV infection who were exposed to telbivudine treatment during pregnancy and analyzed the safety and efficacy of telbivudine during pregnancy. They found that telbivudine exposure during pregnancy women with HBV infection had not increased the rates of live birth defects, spontaneous abortion or elective termination. There were no fetal/neonatal toxicity reported during telbivudine treatment. Telbivudine exposure in the second and/or third trimesters of pregnancy could reduce the risk of HBV transmission from mother to child. The topic is interesting and the manuscript is well-written.

Comments:

However, several problems should be corrected.

1. In page 11, there were a total of 18 publications collected which were listed in Table 3. Actually, there were 21 publications in Table 3.

Response: Thank you for your review comment. In the previous version, some publications appeared in 2 rows of the table. There are 18 publications included in this study. Table 3 has been reformatted to make it easier to understand.

2. "Of the 1673 live births, a total of 6 infants had birth defects". When did telbivudine administrate in these cases?

Response: Thank you for your review comment. Of the 6 infants, 4/6 infants with birth defects were born to mothers starting telbivudine treatment in 1st trimester; 2/6 infants with birth defect were born to a mother starting telbivudine treatment in 2nd or 3rd trimester. Relevant information has been added to the "Results" section.

3. According to the information from antiretroviral pregnancy registry, only 27 patients with telbivudine prophylaxis were included. The sample number might be not enough to conclude that telbivudine exposure during pregnancy women with HBV infection have not increased the rates of live birth defects.

Response: Thank you for your review comment. The APR registry data is only a reference database in our study. The conclusion of our study is not drawn based on the APR data, but based on the 18 literature studies. Our conclusion is based on 1673 mothers treated with telbivudine during pregnancy and we believe it is a solid and evidence based conclusion.

4. There are several grammar errors in the manuscript.

Response: We have addressed your review comment.

5. In the introduction, "tenofovir belong to pregnancy category B". However, relevant researches of tenofovir in pregnancy patients with HBV infection are limited and could not offer enough evidence for the safety of tenofovir. The authors offered mistaken orientation for tenofovir therapy of pregnant patients with HBV infection.

Response: Thank you for your review comment. Tenofovir is a pregnancy catergory B drug per FDA designation and its label. According to EASL CHB guidelines, tenofovir is also recommended as a

pregnancy category B agent. [Source text: "Thus, telbivudine, lamivudine or tenofovir (as a potent FDA category B agent) may be used for the prevention of perinatal and intra-uterine HBV transmission in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (ser

Reviewer's code: 00012216

Teerha Piratvisuth et al carry out a comprehensive review about the efficacy to prevent mother-to-child HBV transmission and about foetal toxicity of telbivudine during pregnancy. The review is well structured and the information summarised is relevant for clinical practice.

Reviewer's code: 00005855

In this review, the authors tried to achieve an evidence-based conclusion regarding the safety and efficacy of telbivudine use in HBV infected pregnant mothers and to confirm the observations from telbivudine preclinical studies. The authors thoroughly collected data and analyzed appropriately pooled data. This review demonstrated the evidence of the safety and usefulness of telbivudine treatment during pregnancy.

Comments:

There are a few issues to be addressed.

1. The authors compared the mother-to-child transmission (MTCT) incidence, and the control incidence was as high as 11.9% in spite of standard immunoprophylaxis. As the authors mentioned, complete and timely sero-vaccination had a low immunoprophylaxis failure rate of 3%. Is the control group appropriately matched with the telbivudine treatment group?

Response: Thank you for your review comment. The control groups in the literature studies have received standard immunoprophylaxis. This immunoprophylaxis failure rate is similar to other Chinese studies. The control groups were matching with the telbivudine treatment group with the only difference of no telbivudine treatment, as reported by the literatures studies.
The immunoprophylaxis failure rate of 3% was reported from an Africa study which is a different ethnic group with our study selected population.

2. There are two reviews on the similar theme as the present one (references #36 and 37). The difference between the present and former reviews other than accumulation of data thereafter should be discussed.

Response: Thank you for your review comment. Although the two earlier reviews, Deng M et al 2012 [Ref. 36] and Xi H et al 2012 [Ref. 37], are similar to the present review, there are some differences. Deng M et al., 2012 reported results from a meta-analysis which provided preliminary evidence that telbivudine application in late pregnancy is effective in the interruption of intrauterine HBV infection. Only 6 studies were included for analysis (2 randomized controlled trials and 4 non-randomized controlled trials) which included 576 mothers. Most of the included studies were performed in China, therefore, clinical studies performed in different populations and regions are missing in the analysis, which is important to access the generalizability of the study results. Xi H et al 2012 paper [Ref. 37] reported results from a meta-analysis which evaluated the efficacy and safety of telbivudine treatment in pregnant patients with chronic hepatitis B to block mother-to-child transmission of hepatitis B virus. Only 8 studies were included in the analysis by Xi H et al. In contrast, 18 studies were included in our analysis. The present review included studies published in 2015 and our study has the largest number of telbivudine treated mothers (n=1725) to date. The report also provides data

from pharmacovigilance reports on telbivudine exposure and the Antiretroviral Pregnancy Registry during pregnancy in women with HBV infection, whereas all these points/features are missing in the earlier two reviews.

3. In Tables 1 and 3, vertical lines and redundant horizontal lines should be removed.

Response: We have reformatted Tables 1 and 3.

Reviewer's code: 00013065

In this interesting review article Dr. Piratvisuth and colleagues aimed to confirm the safety of telbivudine administration in pregnancy and its efficacy in preventing mother-to-child-transmission of HBV infection by analysing the available literature of this topic. Overall, the presented review article is comprehensive, well and appropriate referenced, and yet concise in its content. The authors analyzed appropriately the collected data. The introduction introduces the following sections well. The review article is informative and interesting to read.

Comments:

However, there are some minor comments which should be addressed.

1. The authors have listed two recent comparable review articles on similar topic (references 36 and 37) but didn't discuss what is new of their report.

Response: Thank you for your review comment. Although the two earlier reviews, Deng M et al 2012 [Ref. 36] and Xi H et al 2012 [Ref. 37], are similar to the present review, there are some differences. Deng M et al., 2012 reported results from a meta-analysis which provided preliminary evidence that telbivudine application in late pregnancy is effective in the interruption of intrauterine HBV infection. Only 6 studies were included for analysis (2 randomized controlled trials and 4 non-randomized controlled trials) which included 576 mothers. Most of the included studies were performed in China, therefore, clinical studies performed in different populations and regions are missing in the analysis, which is important to access the generalizability of the study results. Xi H et al 2012 paper [Ref. 37] reported results from a meta-analysis which evaluated the efficacy and safety of telbivudine treatment in pregnant patients with chronic hepatitis B to block mother-to-child transmission of hepatitis B virus. Only 8 studies were included in the analysis by Xi H et al. In contrast, 18 studies were included in our analysis. The present review included studies published in 2015 and our study has the largest number of telbivudine treated mothers (n=1725) to date. The report also provides data from pharmacovigilance reports on telbivudine exposure and the Antiretroviral Pregnancy Registry during pregnancy in women with HBV infection, whereas all these points/features are missing in the earlier two reviews.

2. It is well known that telbivudine will select antiviral resistance. Do the authors have any data concerning emerging of resistance mutations in the selected patients?

Response: Thank you for your review comment. Of the 18 literature studies, 15 studies did not report antiviral resistance associated with telbivudine treatment; 3 studies had reported a resistance rate of 1.2%, 2.3% or 6.5%. Relevant information has been added to the discussion section.

3. The authors reported 18 publications in the "characteristics of the selected cases" section in the text and noted 21 in table 3. Please correct.

Response: In the previous version, some publications appeared in 2 lines. There are 18 publications included in this study. Table 3 has been reformatted to make it easier to understand.