Title: What is the optimal timing of antiviral treatment in pregnant hepatitis B carrier with extremely high viral load ?

Sir,

We appreciate the comments from Vyas et al. (1) Although our study demonstrated that prediction of infants' immunoprophylaxis failure (IF) is possible in early pregnancy, whether women with extremely high viral load require earlier antiviral treatment for prevention of IF remains unknown.(2) Two randomized controlled trials showed no cases of IF (0/239) after the use of tenofovir disoproxil fumarate (TDF) in women with baseline HBV DNA >5.3$\log_{10}$IU/ml in the third trimester. However, when the maternal HBV DNA was > 7.5$\log_{10}$IU/mL at baseline, a 3.1% IF rate (2/65) was noted in a prospective multicenter trial.(3) Therefore, an increased baseline HBV DNA might be associated with higher viral load at delivery and subsequent IF. Furthermore, apart from the maternal HBV DNA level, other clinical factors that affect the timing of starting antenatal TDF treatment include the risk of preterm delivery and the need for prenatal invasive testing. Although current data do not suggest teratogenicity from the early use of TDF during pregnancy, the potential long-term effect of TDF on offspring's mitochondrial function after antenatal antiretroviral treatment would need further evaluation, especially if TDF were started in first or

second trimester of pregnancy.(4)

We suggested using maternal age and body mass index to identify HBV carrier at a higher risk of elevated HBV DNA.(2) Using a high throughput platform for quantifying hepatitis B surface antigen (HBsAg) level might be another option in resource-limited setting. The HBsAg level positively correlated with the HBV DNA level in women with positive hepatitis B e antigen status who usually harbor an elevated HBV DNA. Nonetheless, a suggested level of 4.1$\log_{10}$IU/ml could not pick up all women with high viral load or IF, and prospective studies using HBsAg level to predict IF are currently lacking.(5) We acknowledged the limitations of our observational study and lack of HBV genotyping of our study participants[2].

We agree with Vyas et al. that a well-designed prospective study is required to evaluate the role of earlier antiviral treatment in pregnant HBV carriers with viral load > 7.5$\log_{10}$IU/mL and its the long-term effect on the offspring, preferably in the setting of a randomized controlled trial. This will definitely require an international concerted effort and commitment to achieve complete global elimination of HBV.

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Disclosure

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Reference:

1. Vyas AK. Timing of hepatitis B virus DNA quantification and treatment approach during pregnancy. Acta Obstetricia et Gynecologica Scandinavica. 2019.

2. Cheung KW, Seto MTY, So PL, Wong D, Mak ASL, Lau WL, et al. Optimal timing of hepatitis B virus DNA quantification and clinical predictors for higher viral load during pregnancy. Acta Obstet Gynecol Scand. 2019.

3. Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology. 2015;62(2):375-86.

4. Venhoff N, Walker UA. Mitochondrial disease in the offspring as a result of antiretroviral therapy. Expert Opin Drug Saf. 2006;5(3):373-81.

5. Thilakanathan C, Wark G, Maley M, Davison S, Lawler J, Lee A, et al. Mother-to-child transmission of hepatitis B: Examining viral cut-offs, maternal HBsAg serology and infant testing. Liver Int. 2018;38(7):1212-9.