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Editorial

Postpartum Hepatic Flares in Immune-Tolerant Pregnant Patients with Chronic Hepatitis B Virus Infection

Myeong Jun Song

Division of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Corresponding Author
Myeong Jun Song
ORCID https://orcid.org/0000-0001-5244-0372
E-mail mjsong95@gmail.com

See "Clinical and Immunological Factors Associated with Postpartum Hepatic Flares in Immune-Tolerant Pregnant Women with Hepatitis B Virus Infection Treated with Telbivudine" by Junfeng Lu, et al. on page 887, Vol. 15, No. 6, 2021

Chronic hepatitis B (CHB) is a serious chronic disease affecting 250 million people in the world. Most common risk of developing CHB is vertical or mother-to-child transmission (MTCT) from mothers who are hepatitis B surface antigen positive. To prevent MTCT, World Health Organization recommends active vaccination in childhood with hepatitis B immune globulin.[1] This strategy has showed a significant decline in MTCT and the global incidence of CHB since the 1990s. However, immunoprophylaxis failure was observed approximately 10% in case of maternal hepatitis B virus (HBV) DNA levels (more than 9 log10 copies/mL), although this active vaccination strategy has been applied.[1] Therefore, current guidelines recommend antiviral therapy in the third trimester in pregnant women who are high viral load to reduce the risk of MTCT.[2] However, several controversies over antiviral treatment have not been resolved, that is, optimal duration, effect of postpartum therapy, and risk of postpartum alanine aminotransferase (ALT) flare after withdrawal.

In the prvious issue of *Gut and Liver*, Lu *et al.*[3] reported clinical and immunological factors in postpartum hepatic flares in immune-tolerant patients who received peripartum antiviral prophylaxis against MTCT of CHB. In this study, 36.3% had postpartum hepatic flares, defined a 2-fold increase in ALT at 6 weeks after delivery. They suggested risk factors of postpartum hepatic flares are younger age, greater antepartum ALT, and lower postpartum hepatitis B e antigen (HBeAg) titer. In immunologic study, the lower interferon γ (IFN-γ) level during pregnancy and the higher IFN-γ level after delivery were reported to be associated with postpartum hepatic flares. Patients with these characteristics might experience the transition from immune tolerance phase to immune active phase after delivery. Therefore, they suggested younger patients with postpartum hepatic flares accompanied by lower HBeAg level and higher IFN-γ level after delivery may be suitable for further re-antiviral treatment. The strength of this study would be to try to suggest the predictive factors of postpartum hepatic flares and need for extension of re-antiviral therapy in immune-tolerant patients with CHB. It is unknown whether pregnant women with CHB in the postpartum period are at higher risk of immune-mediated flares and progression of liver disease. When immune reconstitution occurs after delivery, hepatic flares with elevated ALT and higher rates of HBeAg loss have been reported, during early postpartum.[4] Most flares are self-limited, but some can be severe liver disease. Therefore, it is an important issue to identify the possible candidates of postpartum hepatic flares.

Pregnancy dynamically changes the maternal immune system and occur to prevent fetus rejection. Regulatory T cell (Treg) frequency in pregnant women is decreased during pregnancy.[5] This decrease may also occur due to maternal Tregs migrating to the maternal–fetal surface to prevent maternal–fetal rejection, resulting in decreased peripheral blood Treg frequency. These alterations reverse rapidly after delivery. Huang *et al.*[6] found that the characteristics of T cell immunity was distinct between flares and non-flares mothers from pregnancy to postpartum. T cell immunity in mothers with ALT flares was characterized by lower Treg frequency and higher ratio of pro-inflammatory cytokine to anti-inflammatory cytokine in CD4+ or CD8+

T cells. Maternal immune status might play an important role in postpartum ALT flare in HBV-infected mothers. Thus, the HBV-infected mothers with postpartum hepatic flare should be monitored closely.

Previous studies suggested high HBV DNA level at delivery and withdrawal of antiviral treatment as potential risk factors for postpartum flare.[7,8] Postpartum flare occurs in 25% to 44.7% and mainly happens for 3 months postpartum.[8] HBV DNA is the most important viral marker for predicting HBV MTCT risk, maternal liver disease progression, and need for antiviral therapy in pregnancy. Yi *et al.*[7] reported that HBV DNA at delivery is a predictive factor of postpartum flare. However, other studies including this study showed HBV DNA levels were not linked to flares.[9] Further study is needed in the meaningful role of HBV DNA in postpartum ALT flares. Withdrawal of antiviral agent may be another risk factor of hepatic flare. Mothers with elevated ALT during pregnancy showed higher postpartum flare rate compared with those without ALT elevation (25% vs 11.9%).[8] Withdrawal of antiviral therapy should be prudential for mothers with elevated ALT during pregnancy and consider extending antiviral treatment.

We should keep in mind that biochemical flares can occur in postpartum in mothers with CHB treated with antiviral therapy and maternal postnatal monitoring for exacerbations of liver disease is necessary. We also need to understand the limitations of this study in special population and as a clinical unmet need to be solved in pregnant patients in the future. First, there is no generally accepted definition of postpartum flare. Authors used a 2-fold increase in ALT to define hepatic flare in this study. Recent studies have used liberal definitions for ALT flares; any ALT >upper normal limit (UNL); or an ALT >2 or 5 times UNL. These differing definitions of ALT flares make comparisons between studies difficult. Although different criteria of postpartum hepatic flare were defined, tenofovir disoproxil fumarate (TDF) study in HBV mothers with high viral load showed ALT elevations above the normal range (45%) after the discontinuation of TDF.[10] It seems to be no difference between telbivudine and TDF in postpartum hepatic flares. Second, follow-up after delivery was short in this study. Guidelines recommend HBV-infected pregnant women should be monitored closely for up to 6 months after delivery for hepatic flare because the timing of postpartum flare is different on each study.[2] Therefore, it is necessary to investigate the rate of postpartum flares in further period. Finally, there is still a lack of meaningful immunological data to support altered immune activity in pregnancy and postpartum. Until now, the change of ALT, HBeAg status, and HBV DNA level are only marker to identify the natural history of CHB in clinical practice. It is difficult to differentiate the transition from immune-tolerant to immune clearance phase in patients during postpartum period. Thus, additional studies on novel HBV biomarkers including HBeAg titer and relevant host immunologic markers are needed to evaluate their prognostic and diagnostic potential in management of patients with CHB in pregnancy and postpartum.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Myeong Jun Song https://orcid.org/0000-0001-5244-0372

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