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Editorial

Third-trimester tenofovir to prevent mother-to-child hepatitis B virus transmission

Worldwide, chronic hepatitis B virus (HBV) remains a leading cause of cirrhosis and liver cancer. Prevention of transmission and thereby chronic infection is considered the most effective public health intervention to minimize the global burden of HBV and its disease-related complications. Despite vaccination, mother-to-child transmission (MTCT) of HBV remains an important source of chronic infection in endemic areas. The risk of developing chronic HBV infection is inversely proportional to age at the time of exposure, and the risk is as high as 90 per cent for those exposed at birth[1,2]. The combination of postnatal passive (*i.e.* vaccination) and active [*i.e.* hepatitis B immunoglobulin (HBIG)] immunization significantly reduces neonatal transmission rates. However, appropriate immunoprophylaxis fails to protect approximately 10 per cent of infants born to mothers at highest risk for transmission from chronic infection[3,4].

There is a growing body of literature to support use of antiviral therapy late in pregnancy to reduce risk of breakthrough neonatal infections among women at increased risk for neonatal transmission, such as those with hepatitis B e antigen (HBeAg)-positive disease who have high levels of HBV DNA in serum[5]. Maternal serum HBV DNA titre appears to be directly related to risk for MTCT[6,7]. While an exact threshold of risk is difficult to quantify, there appears to be general consensus that the risk is significantly higher if maternal HBV DNA exceeds 200,000 IU/ml (>10^6 copies/ml) at the time of delivery[8,9]. It is currently recommended that hepatitis B surface antigen (HBsAg)-positive mothers have serum HBV DNA quantification toward the end of the second trimester (wk 26-28 gestation), to allow for the initiation of third-trimester therapy if indicated after a thorough discussion of risks and benefits. Antiviral therapy can then be stopped post-partum with careful monitoring for disease activity in patients who do not otherwise meet criteria for chronic HBV treatment.

There are limited prospective randomized controlled trials (RCTs) examining the efficacy of antiviral therapy in pregnancy for the prevention of transmission. A recent meta-analysis of 26 studies concluded that antiviral therapy (in addition to passive-active immunization) reduced the risk of HBV transmission (risk ratio 0.3, 95% confidence interval 0.2-0.5) with no increased risk of adverse outcomes; however, the quality of available data was poor overall, with a dearth of prospective data or RCTs[5]. Three antiviral agents have been studied and are considered acceptable for use in pregnancy[5,9-14]. Much of the clinical safety data for HBV antivirals pertain to tenofovir and lamivudine because these agents are also used in HIV, and since 1989, the Antiretroviral Pregnancy Registry (APR)[15] has been evaluating the teratogenic effects of HIV agents and confirmed that birth defect rates from lamivudine or tenofovir exposure were comparable to those seen in the general population[16]. Telbivudine is also considered safe and effective, though based on a relatively limited number of short term trials, and less rigorous safety data[5,11,13]. Entecavir and adefovir, also used to treat chronic HBV, have inadequate safety data in pregnancy and should not be used in this setting. In practice, tenofovir is generally preferred for use for MTCT prevention in late pregnancy given rapid viral load reduction and efficacy, tolerability, and minimal risk of viral resistance if required for longer term use[12,14,17,18].

Much of the clinical data regarding third-trimester tenofovir use are derived from cohort and observational studies. Chen *et al*[12] assessed the efficacy of tenofovir in reducing MTCT in a non-randomized prospective study of 118 e-antigen positive Taiwanese women

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with high viral load (HBV DNA >$10^{7.5}$ IU/ml) who received either standard of care or tenofovir in the third trimester until one month post-partum. They concluded that tenofovir was efficacious overall: only one of 65 treated infants was HBsAg positive by six months, compared to six of 65 untreated (1.54 vs. 10.71%, *P*=0.0481). However, on long term follow up, a second child was found to be HBV-infected, which ultimately resulted in similar rates of MTCT as compared to the untreated group at the end of the study[12].

To further address the question of third-trimester antiviral safety and efficacy, Pan *et al*[14] have contributed the first RCT comparing tenofovir to standard care for preventing MTCT among mothers with high viral load. In this trial, 200 HBeAg-positive mothers with HBV DNA level >200,000 IU/ml were randomly assigned to receive standard care without antiviral therapy or to receive a 300 mg oral dose of tenofovir [tenofovir disoproxil fumarate (TDF)] from 30 to 32 wk gestation to post-partum week four and were followed to postpartum wk 28. All infants received immunoprophylaxis: 200 IU of HBIG intramuscular and 10 µg of HBV vaccine within 12 h of birth, followed by two subsequent vaccine doses, as per the World Health Organization guidelines[19]. At delivery, 68 per cent of mothers in the tenofovir-treated group had an HBV DNA level <200,000 IU/ml as compared to two per cent of the control group. At post-partum wk 28, the rate of MTCT was significantly lower in the tenofovir-treated group as compared to controls for both the intention-to-treat analysis (5 vs. 18%, *P*=0.007) and the per-protocol analysis (0 vs. 7%, *P*=0.01). There were no neonatal infections among treated mothers. In addition, there was no significant difference in the maternal and infant safety profiles including congenital disabilities. A higher proportion of women had elevation of the alanine aminotransferase (ALT) levels after discontinuation of TDF than untreated women (45 vs. 30%, *P*=0.03). The authors concluded that tenofovir safely reduced the rates of MTCT, supporting a key role of third-trimester antiviral therapy in a larger randomized trial of high-risk women.

This quality trial provides further clinical data regarding the safety and efficacy of tenofovir in pregnancy; however, additional research is needed to elucidate the optimal timing of antiviral initiation. In this study[12], 68 per cent of mothers who started treatment between 30 and 32 wk achieved HBV DNA <200,000 IU/ml by delivery, suggesting that nearly one-third of women continued to have levels above the HBV DNA threshold defined as conferring high risk for transmission. Some have suggested that antiviral prophylaxis should start earlier to maximize the likelihood of suppressed HBV DNA at the time of delivery, accounting for potentially early births[13,14]. However, the risks of earlier foetal exposure have not been assessed against the risk of prophylaxis failure.

The majority of our evidence regarding safety of antivirals and in particular, tenofovir during pregnancy is derived from the APR data, documenting safety of antivirals in the setting of HIV infection, when used throughout pregnancy[15]. These registry data suggest that the rate of congenital disabilities among infants with exposure to tenofovir (2.4%) was similar to the rate in the general population[16]. The limitations of the APR include underreporting and lack of long-term follow up of infants. There have been more reports of lower bone mineral content in newborns exposed to tenofovir throughout pregnancy among HIV-infected women[20]. In theory, use of antiviral therapy in the third trimester should ameliorate risks of teratogenicity. However, a study showed that mean bone mineral content was 12 per cent lower in the third-trimester tenofovir-exposed infants as compared to controls[21]. The long-term clinical significance of this finding is unclear and requires further study. Tenofovir alafenamide (TAF) is a prodrug of TDF that has similar antiviral efficacy at lower doses and results in lower tenofovir concentrations in blood, with improved renal and bone safety parameters. However, TAF is not yet approved for the use in pregnancy. Despite favourable safety profiles for select agents, for the purposes of reducing MTCT, antiviral therapy should be initiated later in pregnancy, thus minimizing potential risk associated with foetal exposure.

Transmission of HBV through breastfeeding is considered low risk in infants who receive immunoprophylaxis, and breastfeeding for HBV-positive mothers is recommended. On the other hand, oral nucleos(t)ide analogues have been shown to be excreted in breast milk, and there are relatively limited data regarding the effect of these antivirals on infants. In the study by Pan *et al*[14], women were instructed not to breastfeed for the first four weeks post-partum until drug discontinuation. Accumulating evidence from HIV-positive mothers suggests that infant exposure to tenofovir in breast milk is minimal and not associated with adverse effects[15,22]. However, there are relatively limited data on the safety of tenofovir use during breastfeeding among HBV-infected women from

existing trials. These issues highlight the importance of a clear discussion with patients of the risks and benefits of initiating antiviral therapy during pregnancy and continuation thereafter.

In the management of pregnant women with chronic HBV infection, the risks and benefits for both the mother and infant should be considered independently when deciding on antiviral therapy. The majority of HBV-infected women of childbearing age have mild disease, and the treatment is often not indicated given low levels of inflammation and/or liver fibrosis. While identification of patients at high risk for transmitting chronic infection to their infant is an important goal, it is also critical to identify and treat HBV among women of childbearing age at risk for liver-related complications who would benefit from longer term antiviral therapy, regardless of their pregnancy status. On the other hand, for women who become pregnant while taking HBV antivirals, there are risks to stopping therapy for those who have clear indications for treatment but desire to minimize foetal exposure to HBV medications. Unless continued for the clinical benefit of the mother, antiviral therapy can be withdrawn immediately in the post-partum period. Upon discontinuation at any point during or after pregnancy, women should be monitored carefully for HBV disease flares. In a prior report, ALT flares following antiviral withdrawal were common[23]. In the study by Pan *et al*[14], elevation in ALT was observed more often in the treatment group and 89 per cent had viral rebound after stopping therapy, although there were no clinically significant disease flares or cases or genotypic resistance. It is not clear whether women themselves benefit from short-term third-trimester therapy, and further data supporting the optimal timing and potential risk of antiviral discontinuation are needed.

The burden of chronic HBV varies significantly worldwide. The greatest relevance of this topic is clearly in highly endemic countries such as China, where a >8 per cent prevalence of chronic infection is found, and 5-10 per cent of chronic infections are estimated to occur through MTCT[24]. The prevalence of chronic HBV infection in India ranges from 2 to 4 per cent, defined as low-intermediate endemicity[24-26]. The available data suggest that <1.5 per cent of pregnant women in India are HBV-infected, yet estimates vary widely, and the burden of chronic infections secondary to MTCT is unknown and may be underestimated[27,28].

In summary, the management of HBV infection in pregnancy needs to be individualized and the risks of treatment need to be considered individually for both the mother and foetus, as well as the benefits to the neonate; in addition, the risk of discontinuation of therapy after delivery needs to be weighed for the mother versus the potential risks of neonatal exposure to antiviral therapy via breast milk. Pan *et al*[14] have contributed the first RCT of tenofovir, a preferred first-line agent, for use in the third trimester to reduce MTCT risk without compromising maternal or foetal safety. However, additional information is needed to determine the optimal threshold for antiviral therapy, timing of initiation and withdrawal, benefit to the mother and longer term safety for neonates.

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References

1. Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, *et al.* Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. *Gastroenterology* 2012; *142* : 773-81.e2.
2. Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, *et al.* Prevention of vertical transmission of hepatitis B: An observational study. *Ann Intern Med* 2014; *160* : 828-35.
3. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, *et al.* Perinatal transmission of hepatitis B virus: An Australian experience. *Med J Aust* 2009; *190* : 489-92.
4. Pan CQ, Duan ZP, Bhamidimarri KR, Zou HB, Liang XF, Li J, *et al.* An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. *Clin Gastroenterol Hepatol* 2012; *10* : 452-9.
5. Brown RS Jr., McMahon BJ, Lok AS, Wong JB, Ahmed AT, Mouchli MA, *et al.* Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology* 2016; *63* : 319-33.
6. Wen WH, Chang MH, Zhao LL, Ni YH, Hsu HY, Wu JF, *et al.* Mother-to-infant transmission of hepatitis B virus infection: Significance of maternal viral load and strategies for intervention. *J Hepatol* 2013; *59* : 24-30.
7. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis

in infants born to HBsAg-positive mothers. *J Viral Hepat* 2012; *19* : e18-25.

8. Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, *et al.* Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: A 2016 update. *Hepatol Int* 2017; *11* : 1-30.
9. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; *63* : 261-83.
10. Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, *et al.* Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: A multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009; *16* : 94-103.
11. Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, Bai SF, *et al.* A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatol* 2011; *55* : 1215-21.
12. 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* : 375-86.
13. Pan CQ, Han GR, Jiang HX, Zhao W, Cao MK, Wang CM, *et al.* Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. *Clin Gastroenterol Hepatol* 2012; *10* : 520-6.
14. Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, *et al.* Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med* 2016; *374* : 2324-34.
15. Antiretroviral Pregnancy Registry (APR). Available from: *http://www.apregistry.com/HCP.aspx*, accessed on February 19, 2017.
16. Brown RS Jr., Verna EC, Pereira MR, Tilson HH, Aguilar C, Leu CS, *et al.* Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: Findings from the Antiretroviral Pregnancy Registry. *J Hepatol* 2012; *57* : 953-9.
17. Chan HL, Chan CK, Hui AJ, Chan S, Poordad F, Chang TT, *et al.* Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. *Gastroenterology* 2014; *146* : 1240-8.
18. Heathcote EJ, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, *et al.* Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011; *140* : 132-43.
19. World Heatlh Organization. Hepatitis B vaccination recommendations for infants, children, and adolescents. *MMWR Morb Mortal Wkly Rep* 2005; *54* (RR-16) : 7-8.
20. Siberry GK, Jacobson DL, Kalkwarf HJ, Wu JW, DiMeglio LA, Yogev R, *et al.* Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis* 2015; *61* : 996-1003.
21. Greenup AJ, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, *et al.* Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *J Hepatol* 2014; *61* : 502-7.
22. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. *AIDS* 2017; *31* : 213-32.
23. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology* 2014; *60* : 468-76.
24. World Health Organization. WHO Fact Sheet. Available from: *http://www.who.int/mediacentre/factsheets/fs204/en/*, accessed on February 19, 2017.
25. Lodha R, Jain Y, Anand K, Kabra SK, Pandav CS. Hepatitis B in India: A review of disease epidemiology. *Indian Pediatr* 2001; *38* : 349-71.
26. Puri P. Tackling the hepatitis B disease burden in India. *J Clin Exp Hepatol* 2014; *4* : 312-9.
27. Dwivedi M, Misra SP, Misra V, Pandey A, Pant S, Singh R, *et al.* Seroprevalence of hepatitis B infection during pregnancy and risk of perinatal transmission. *Indian J Gastroenterol* 2011; *30* : 66-71.
28. Alexander AM, Prasad JH, Abraham P, Fletcher J, Muliyil J, Balraj V. Evaluation of a programme for prevention of vertical transmission of hepatitis B in a rural block in southern India. *Indian J Med Res* 2013; *137* : 356-62.