Hepatology International (2018) 12:94–96
https://doi.org/10.1007/s12072-018-9863-0

EDITORIAL

Prevention of mother-to-child transmission: the key of hepatitis B virus elimination

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Received: 19 February 2018 / Accepted: 27 March 2018 / Published online: 4 April 2018

More than half a century after the initial discovery, hepatitis B virus (HBV) is one of the most common viral infections in humans. With a global heterogeneous prevalence, the HBV epidemic remains a monumental threat of health. In Asia, most HBV patients acquire the virus perinatally or in early childhood and develop a life-long chronic infection [1]. The mechanisms of vertical HBV transmission include intrauterine infection and transmission during delivery [2]. For example, the prevalence of chronic HBV infection in the general population ranged 11–20% in Taiwan during 1980s [3]. Approximately, 40% of HBV carriers were born to HBsAg-positive mothers and 85–95% of newborns with HBV exposure consequently had chronic infection [4]. Thus, mother-to-child transmission (MTCT) during the perinatal period is the major transmission route of HBV in hyperendemic areas [1]. Prevention of MTCT is thus the most important strategy to reduce the global burden of HBV infection.

Immunoprophylaxis with the combination of hepatitis B immunoglobulin and hepatitis B vaccine in newborns has been documented to prevent perinatal HBV transmission. Currently, universal infant HBV vaccination has been implemented in 180 countries worldwide [5]. In Taiwan, the first country to launch a nationwide universal hepatitis B vaccination program [6], the HBV exposure rate (anti-HBc positivity) decreased from 38 to 4.6% in children after implementation of universal hepatitis B immunization [7]. Of particular note is that the HBV carriage rate in infants and children remarkably declined up to 90% in 2012 [8]. Similarly, the prevalence of HBV infection in children was also reduced in different parts of the world after successful implementation of universal hepatitis B immunization [9]. In addition to preventing HBV infection of infants, immunoprophylaxis implementation also reduces hepatocellular carcinoma (HCC) in children, teenagers and young adults [10, 11]. In Taiwan, the incidence of HCC in children decreased from 0.92 per 100,000 in the unvaccinated cohort to 0.23 per 100,000 in the vaccinated birth cohorts [11].

These encouraging data provide the convincing evidence that prevention of HBV infection is the primary strategy for global HBV eradication. However, the immunoprophylaxis failure due to HBV carrier mothers with a high viral load is a great challenge. A cohort study from Taiwan revealed that an increased risk of MTCT was correlated with a high maternal viral load [12]. To enhance the blocking rate of MTCT, antiviral therapy with nucleos(t)ide analogs (NAs) in pregnancy should be considered.

In this issue, He et al. presented the safety and efficacy of lamivudine or telbivudine treatment initiated at the first trimester of pregnancy in mothers with a high viral load [13]. The authors retrospectively enrolled 94 highly viremic mothers, and 49 (52.1%) of them initiated lamivudine or telbivudine in the first trimester of pregnancy. At postpartum week 28, the MTCT rate was significantly reduced in the mothers with NAs treatment than those without (0/61 or 0% vs 4/34 or 11.76%, $p = 0.028$). Of note, the birth defect rates of infants were similar between the treatment group and the control group. These findings indicated that

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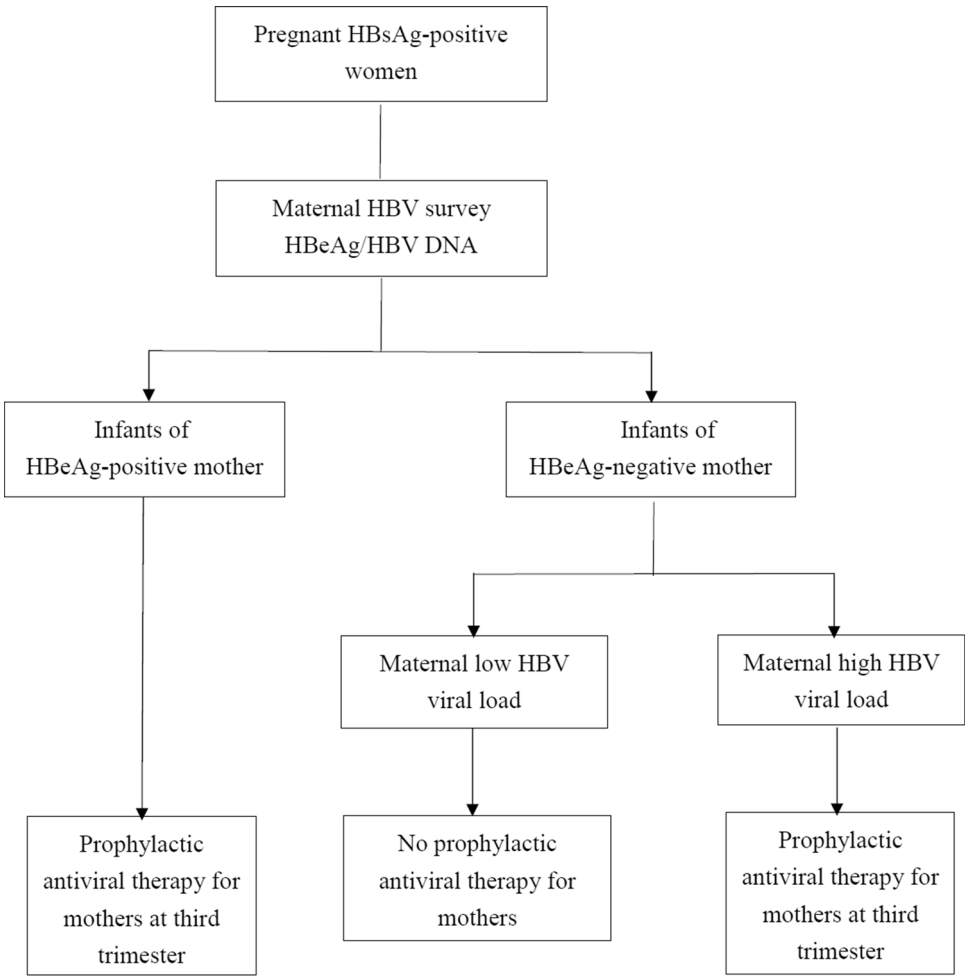

Fig. 1 A proposed algorithm of prophylactic antiviral therapy for pregnant HBsAg-positive female to prevent mother-to-child transmission (MTCT) of HBV. Maternal serum HBV DNA level of 20,000 IU/ml as the threshold of low and high maternal viral load. All infants born to HBsAg-positive female should also receive immunoprophylaxis of hepatitis B vaccination with or without hepatitis B immunoglobulin after birth. *HBV* hepatitis B virus, *HBsAg* hepatitis B surface antigen, *HBeAg* hepatitis B e antigen

lamivudine or telbivudine treatment for mothers with a high viral load in early pregnancy appears to be safe and effective for the interruption of MTCT. However, several issues are worthy of discussion. First, antiviral agents and immunoprophylaxis that are used in preventing MTCT are complementary to each other. In contrast to previous studies, a recent randomized, double-blind clinical trial has shown no additional effect of tenofovir disoproxil fumarate (TDF) in preventing MTCT [14]. In this study, the timely administration of hepatitis B immunoglobulin and hepatitis B vaccine may reduce the requirement of antiviral prophylaxis. However, the timely and complete immunization with hepatitis B immunoglobulin and vaccine remain a challenge in real world practice. Antiviral prophylaxis is considered to provide complementary effect in preventing MTCT.

Second, the optimal timing to start antiviral therapy during pregnancy remains debatable. The main concerns include the effect of HBV DNA suppression at delivery and possible adverse effects of antiviral agents on the infants. In two recent studies, tenofovir disoproxil fumarate (TDF) 300 mg daily was prescribed from 30 to 32 weeks of gestation until 1 month postpartum in highly viremic HBV mothers. Compared to the mothers without antiviral prophylaxis, the mothers who received TDF had a significantly lower rate of infant HBsAg positivity [15, 16]. The safety profiles of infants, including birth defect and prematurity, were comparable between mothers with and without TDF prophylaxis. These findings were further confirmed in a meta-analysis, which demonstrated that any antiviral therapy in the third trimester of pregnancy has profound HBV suppression to reduce MTCT in mothers with a high viral load [17]. Because none of the NAs has been approved for use in pregnancy, the safe profiles for NAs initiated in first trimester pregnancy should be cautious and deserve more studies.

The final issue is to define the indication of initiating treatment of HBV in pregnant women. In a retrospective study of 2356 children, the offspring of HBeAg-positive mothers had significant higher risk for chronic HBV infection than those of HBeAg-negative mothers (9.26 vs. 0.23%, $p < 0.001$) [18]. A prospective study from Taiwan further demonstrated that maternal viral load was significantly associated with the risk of HBV transmission. The

estimated predictive rate of MTCT at maternal viral load level of 5 $\log_{10}$ copies/ml was 0.9%. Surprisingly, the rates of MTCT increased sharply for every log increase in maternal viral load [12]. Similarly, a recent study of 1177 mother–infant pairs also indicated that higher maternal viral loads were associated with a higher risk of MTCT [19]. In the current study, the mothers in the immune tolerant phase of CHB were excluded [13]. The characteristics of immune tolerant phase entail HBeAg positivity and very high serum HBV DNA levels, thus these females have the highest risk of MTCT. Therefore, all infants born to HBsAg-positive female should also receive immunoprophylaxis of hepatitis B vaccination with or without hepatitis B immunoglobulin after birth. Furthermore, maternal serum HBV DNA level of 5 $\log_{10}$ copies/ml (20,000 IU/ml) may serve as an indication for prophylactic antiviral therapy to prevent MTCT, irrespective of HBeAg status (Fig. 1).

In summary, the combination of immunoprophylaxis in newborns and antiviral prophylaxis for mothers with a high viral load is plausible to completely interrupt MTCT of HBV [20]. In addition, existing potent NAs have remarkably improved the disease control of chronic hepatitis B. With the complete interruption of MTCT and a successful functional HBV cure, the mission of HBV elimination would be achievable by 2030 [21].

Compliance with ethical standards

Conflict of interest Chih-Lin Lin and Jia-Horng Kao have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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