Pediatr Gastroenterol Hepatol Nutr. 2020 Jul;23(4):311-318
https://doi.org/10.5223/pghn.2020.23.4.311
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Review Article

Check for updates

Elimination of Mother-to-Infant Transmission of Hepatitis B Virus: 35 Years of Experience

Fang-Ting Lu [1] **and Yen-Hsuan Ni** [2,3]

[1]Department of Pediatrics, Changhua Christian Hospital, Changhua, Taiwan
[2]Department of Pediatrics, National Taiwan University Children's Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan
[3]Hepatitis Research Center, National Taiwan University Children's Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

OPEN ACCESS

Received: Dec 28, 2019
1st Revised: Feb 24, 2020
2nd Revised: May 5, 2020
Accepted: May 23, 2020

Correspondence to
Yen-Hsuan Ni
Department of Pediatrics, National Taiwan University Children's Hospital, 8 Chung-Shan South Road, Taipei, Taiwan.
E-mail: yhni@ntu.edu.tw

ORCID iDs
Fang-Ting Lu
https://orcid.org/0000-0001-5457-9060
Yen-Hsuan Ni
https://orcid.org/0000-0002-1158-5249

Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Chronic hepatitis B viral (HBV) infection remains a major health threat, especially in high-prevalence areas. Most infants infected by mother-to-infant HBV transmission become chronic carriers. In Taiwan, many important preventive interventions have been implemented to block the perinatal transmission of HBV in the past 35 years. The first nationwide universal HBV vaccination program was launched in Taiwan in July 1984. The three-dose HBV vaccine completion rate reached 98.1% in 2018. The prevalence of Hepatitis B surface antigen (HBsAg) decreased from 9.8% in pre-vaccinated period in 1984 to 0.5% in the vaccinated cohort in 2014. The incidence of hepatocellular carcinoma in children aged 6–9 years significantly declined from 0.52 to 0.13 per 100,000 children born before and after 1984, respectively. Furthermore, we have performed a maternal HBV screening program during pregnancy since 1984, with the screening rate peaked at 93% in 2012. The HBsAg- and HBeAg-seropositive rate in pregnant women declined from 13.4% and 6.4% in 1984–1985 to 5.9% and 1.0% in 2016, respectively. To closely control perinatal HBV infection, we have administered hepatitis B immunoglobulin immediately after birth and checked the serum level of HBsAg and anti-HBs in high-risk babies born to HBsAg-seropositive mothers, irrespective of their HBeAg status, since July 2019. We have also adopted short-term antiviral treatments such as tenofovir 300 mg daily in the third trimester for highly viremic mothers and reduced the perinatal infection rates from 10.7 to 1.5%. Through all these efforts, we expect to meet the global goal of eliminating HBV infection by 2030.

Keywords: Hepatitis B; Hepatitis B vaccines; Mother-to-infant transmission

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health threat, especially in high-prevalence areas such as the Western Pacific region and Africa. HBV infection in endemic areas mainly occurs in infancy or early childhood, which leads to high rates of chronicity. Although most young carriers are asymptomatic, life-threatening complications such as liver cirrhosis and hepatocellular carcinoma (HCC) can occur years later. In 2015, viral hepatitis resulted in 1.34 million deaths worldwide, with an estimated 720,000 and 470,000 deaths due to liver cirrhosis and HCC, respectively [1]. In 2016, the World Health Assembly endorsed the first

global health strategy for viral hepatitis, which aims to reduce hepatitis-related mortality and the incidence of hepatitis by 65% and 90%, respectively, by 2030 [2].

HBV vaccination is the most cost-effective method for eliminating HBV infection. Universal vaccination in infancy could prevent perinatal and horizontal transmission of HBV. By the end of 2015, global coverage of the three-dose HBV vaccine during infancy reached 84% [1]. Three major interventions that help reduce HBV transmission are birth dose vaccinations, hepatitis B immunoglobulin (HBIG), and early antiviral prophylaxis for pregnant women with high HBV viremia in the third trimester. In addition, improving the safety of blood transfusions and injections, ensuring that testing is accessible, and treating chronic HBV have also been suggested by the World Health Organization (WHO) as methods for eliminating HBV infection [3].

TIMING OF HBV INFECTION

Perinatal transmission, i.e., transmission from a hepatitis B surface antigen (HBsAg)-carrying mother with positive hepatitis B e-antigen (HBeAg) to the infant, leads to a 90% risk of chronic HBV infection if left un-immunized [4]. Unsterilized syringes, intrafamilial spread among highly infectious family members, and poor hygiene practices can cause horizontal transmission [5]. The chronicity rate decreases as the age at acquisition increases, with a rate of approximately 25–50% in children less than 5 years old and less than 10% in adolescents and adults [6,7]. This indicates that the age at HBV acquisition critically affects patient outcomes. Therefore, the HBV vaccination schedule should be completed as early as possible.

HBV VACCINATION IN TAIWAN

HBV vaccination was first introduced in the 1980s and has been recommended by the WHO since 1992 [8]. By the end of 2017, universal infant HBV vaccination had been adopted in 187 countries. The first national universal HBV vaccination program was introduced in Taiwan on July 1, 1984. During the first 2 years of this program, only newborns of high-risk mothers who were seropositive for HBsAg were vaccinated. The newborns of highly infectious mothers (HBeAg-positive or high HBsAg titer) received an additional 0.5 mL (100 IU) of HBIG within 24 hours of birth. After July 1986, the HBV vaccination program was extended to all newborns with a plasma-derived HBV vaccine at 0, 1, 2, and 12 months of age. Preschool children who had not been vaccinated against HBV in infancy were vaccinated during 1987–1989. All elementary school children also received HBV vaccinations during 1988–1990. The vaccine record of every first-grade student in elementary school was checked, and a “catch-up” dose was administered to those who had not received all of the required doses. The program was extended to all children and adolescents aged 10–19 years during 1989–1991 and adults aged ≥20 years during 1990–1993 on a fee-for-service basis. After 1992, the HBV vaccine was changed to a recombinant yeast vaccine with a new schedule, with vaccinations occurring at less than 1 week, 1 month, and 6 months of age [7]. The expenses of all vaccines and HBIG were covered by the government. Approximately 92% of infants born between 1984 and 2002 received three or more doses [7]. The three-dose completion rate was 98.1% in 2018, demonstrating the high national vaccination coverage rate in Taiwan.

https://doi.org/10.5223/pghn.2020.23.4.311

HBIG FOR PREVENTING PERINATAL TRANSMISSION

The most economical and efficient program to prevent HBV infection in high-risk neonates is a standard dose of 5-μg HBV vaccine plus one dose of HBIG at birth [7]. The HBsAg-seropositive rate of pregnant women in Taiwan was 15–17% between 1996 and 2005 [9,10], and passive immunization with HBIG is funded by the government to prevent perinatal transmission. Newborns of HBeAg-positive mothers received additional 0.5 mL of HBIG within 24 hours of birth between July 1984 and June 2019. Although the administration of HBIG to infants born to HBeAg-negative mothers did not appear to significantly reduce the rate of chronic HBV infection (1.88% vs. 0.99%), it might prevent infantile fulminant hepatitis [11]. The costs associated with HBeAg testing in all pregnant women and pediatric fulminant hepatic failure (FHF) could outweigh the costs of administering HBIG to infants born to HBsAg(+) mothers, irrespective of the mothers' HBeAg status [12]. As the HBV carrier rates continue to decline in Taiwan, the cost-to-benefit ratio will increase. In view of this, the HBIG vaccination policy was changed to include all HBsAg-positive mothers regardless of their HBeAg status in July 2019. In addition, the serum levels of HBsAg and anti-HBs in babies born to mothers with HBV are now assessed when they are aged 1-year-old.

EFFECT OF HBV UNIVERSAL VACCINATION

Decrease in the prevalence of chronic HBV infection

Before the implementation of the universal HBV vaccination program, the rate of chronic HBV carriers (positive HBsAg) was up to 15–20% in the general population of Taiwan. To monitor and evaluate the effectiveness of the nationwide HBV vaccination program, a series of serologic surveys to compare the seroprevalence of the birth cohort before and after the implementation of the universal infant HBV vaccination program in Taipei City, Taiwan, were conducted. The first survey was a baseline study conducted just before the launch of the universal program in 1984 [13], and further seroepidemiologic surveys were conducted every 5 years in 1989 [14], 1994 [15], 1999 [16], 2004 [17], 2009 [18], and 2014 [19]. In people ≤30 years of age, the seroprevalence of HBsAg decreased from 9.8 to 0.5% in Taipei City after 30 years of mass vaccination [19]. In the 6th study, the seropositive rates for antibodies to HBsAg (anti-HBs) and hepatitis B core antibody (anti-HBc) were 47.4% and 4.5%, respectively, in the birth cohort after the vaccination program was launched. These results indicate that Taiwan is moving from an epidemic HBV area to a low endemic area. The global goal of reducing the prevalence of HBsAg set by the WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021 was to reduce the prevalence of HBsAg among children aged 5 years to ≤1% by 2020 [20]. Taiwan has already surpassed this goal. In 2008, Lu et al. [21] conducted a study to investigate HBV vaccine-conferred immunity in adulthood. Anti-HBs were below the protective level in 50–60% of adolescents after a complete vaccination program (anti-HBs <10 mIU/mL), and at least 10% of the fully vaccinated individuals had lost their HBV vaccine-conferred booster response [4]. According to these serial seroepidemiological studies, there was no increase in the seroprevalence of HBsAg with age. This means that the risk of chronic HBV infection does not increase with age, and there is no need to provide a universal booster dose to the general population [19].

Decrease in the incidence of infant fulminant hepatitis

HBV infection is the leading cause of fulminant hepatitis in children living in hyperendemic areas. The mortality rate of infantile fulminant hepatitis with HBV infection was found

https://doi.org/10.5223/pghn.2020.23.4.311

to be 65% [22]. Up to 79% of their mothers were seropositive for HBsAg but seronegative for HBeAg [11]. The annual mortality rate of infantile fulminant hepatitis for infants born between 1975 and 1984 was 5.36 per 100,000 infants and 1.71 per 100,000 infants for those born between 1985 and 1998 [23]. One nationwide study of pediatric FHF in patients aged 1 month to 15 years who had received HBV vaccination showed that 61% of patients with FHF in Taiwan were infants and HBV infection accounted for 57% of these infantile FHF cases [24]. The mortality of infantile fulminant hepatitis in the vaccinated birth cohort decreased by ≥90% from 1977–1980 to 2009–2011. HBV infection is no longer prevalent in the vaccinated cohort, which might be attributed to increased individual and herd immunity [25].

Decrease in the incidence of HCC

HBV infection is the leading cause of HCC, especially in children. Of children with HCC in Taiwan, 80–90% were HBsAg-seropositive, confirming the close relationship between HBV infection and pediatric HCC [26,27]. Prevention of HCC by HBV vaccination has been supported by decreased childhood HCC rates in Taiwan after the introduction of the nationwide vaccination program. The incidence of HCC in children aged 6–9 years significantly declined from 0.52 to 0.13 per 100,000 in children born before and after 1984, respectively [28]. The cancer prevention effect of universal HBV vaccination in reducing the incidence of HCC has been extended to young adults aged 20–26 years [27]. Compared with the unvaccinated birth cohort, the HCC incidence rate declined by more than 80% in individuals aged 5–29 years [25]. However, some individuals in the vaccinated birth cohort still developed HCC. Among individuals aged 6–26 years with HCC, 87% were HBsAg-seropositive, and 83% had an HBsAg-seropositive mother. This was significantly related to incomplete vaccination and maternal seropositivity for HBsAg and HBeAg [27,29].

MOTHER-TO-INFANT TRANSMISSION

The maternal HBV screening program during pregnancy has existed in Taiwan since 1984. The highest annual maternal screening rate was 93%, which occurred in 2012. The HBsAg and HBeAg seropositivity rates of pregnant women declined from 13.4% and 6.4% in 1984–1985 to 5.9% and 1.0% in 2016, respectively [9]. The HBV carrier rate in pregnant women and burden of perinatal infection significantly decreased. Although vaccination is a safe and effective tool to prevent HBV infection, it still does not completely eradicate mother-to-infant transmission (MTIT). MTIT HBV frequently occurs either in the uterus, through placental leakage, or exposure to blood-contaminated fluids during birth. Most MTIT occurs during delivery, with high maternal viral load and positive maternal HBeAg as the most significant risk factors [30]. The morbidity and mortality of MTIT are much more severe than those of horizontal transmission. In one study, even though all newborns received HBIG within 24 hours of birth plus timely hepatitis B vaccinations, 2.4% subjects were seropositive for HBsAg soon after birth, and all had chronic HBV infection [31]. The immunoprophylaxis regimen fails in approximately 10% of children with HBeAg-positive mothers [11]. Infants born to mothers who are HBeAg-positive and with higher HBV viral loads are at risk of developing chronic infection. The predictive rates of HBV infection at maternal viral load levels of 10^7, 10^8, and 10^9 copies/mL were 6.6%, 14.6%, and 27.7%, respectively [30]. These findings justify the use of antiviral agents in pregnant women who have a high risk of viral transmission.

https://doi.org/10.5223/pghn.2020.23.4.311

Antiviral prophylaxis treatment in HBV-infected pregnant women to minimize perinatal transmission

Antiviral nucleos(t)ide therapy in late pregnancy is a safe and effective method to reduce MTIT and has been recommended by a number of international expert societies [32-34]. Lamivudine, telbivudine, and tenofovir disoproxil fumarate (TDF) are the only antiviral agents that have been studied in pregnant women that can reduce the risk of MTIT of HBV safely [35,36]. A prospective well-controlled, multicenter trial in Taiwan compared MTIT in HBeAg-positive mothers with HBV DNA ≥107.5 IU/mL receiving TDF with those who had standard vaccination alone. The TDF-treated women received 300 mg of TDF daily from 30–32 weeks of gestation until 1 month postpartum. The positivity for HBsAg in 6-month-old infants decreased from 10.7 to 1.5% in the TDF-treated group, with an odds ratio of 0.10 [37]. A 2016 open-labelled randomized controlled trial in China also demonstrated that TDF in pregnant women with high HBV viral loads of $>2\times10^5$ IU/mL resulted in reduction in HBsAg positivity from 18 to 5% (p=0.007) in the intension-to-treat analysis, and a reduction from 7 to 0% (p=0.01) in the per-protocol analysis [38]. Another study from Thailand demonstrated that there was no significant benefit (2% vs. 0%, p=0.12) of TDF over placebo based on the HBsAg-positivity of 6-month-old infants [39]. Jourdain et al. [39] asserted that these conflicting results might be due to two reasons. First, in Thailand, the first dose was administered early (median, 1.2 hours after birth), after which the infants received four boosters at 1, 2, 4, and 6 months of age. Second, a low number of transmissions occurred in this trial (MTIT rates of 2% in the control group and 0% in the maternal tenofovir-treated group). In addition to HBV DNA, maternal HBsAg levels above 10^4 IU/mL are considered as an indication for prescribing treatment to reduce the likelihood of MTIT [40]. In 2019, we demonstrated that children born to pregnant mothers who received TDF treatment in the third trimester had a lower HBV DNA-positive rate at birth (5.2% vs. 30.1%), and lower HBsAg seropositivity at 6 months (1.7% vs. 11.8%) and 12 months (1.7% vs. 10.8%). Neonatal HBV DNA-positive status was highly correlated with pediatric chronic HBV infection (odds ratio, 61.9) [41].

CONCLUSION

Successful prevention of HBV transmission in Taiwan suggests indicates possible elimination of HBV worldwide in the future. To prevent MTIT of HBV, a comprehensive public health program and a medical care system are required. Owing to the efforts of many experts in Taiwan over the past four decades, we have achieved a high coverage rate for three doses of the HBV vaccine and HBIG, high screening rates for HBV markers in pregnant women, and prompt antiviral therapy in highly viremic pregnant women. In addition, high-risk infants are screened for HBV seromarkers when they are aged 1-year-old. The prevalence of HBV infection in Taiwan has considerably decreased since the introduction of a national HBV vaccination program. There has also been a reduction in the prevalence of infantile fulminant hepatitis and HCC. It is expected that there will be a decline in the incidence of chronic liver disease complications and HCC in adults in the future. Despite this success, breakthrough HBV infection in infants with highly infectious mothers remains a significant problem. Antiviral prophylactic treatment in pregnant women with high viremia can help prevent MTIT. In pediatric patients with chronic HBV, HBV therapy aims to decrease hepatic inflammation, reduce viral replication, and accelerate HBeAg seroconversion. Long-term, scheduled follow-ups are needed for children with chronic HBV.

https://doi.org/10.5223/pghn.2020.23.4.311

REFERENCES

1. World Health Organization. Global hepatitis report, 2017. Geneva: World Health Organization, 2017.
2. Smith S, Harmanci H, Hutin Y, Hess S, Bulterys M, Peck R, et al. Global progress on the elimination of viral hepatitis as a major public health threat: an analysis of WHO Member State responses 2017. JHEP Rep 2019;1:81-9.
PUBMED | CROSSREF
3. Hutin YJ, Bulterys M, Hirnschall GO. How far are we from viral hepatitis elimination service coverage targets? J Int AIDS Soc 2018;21(Suppl 2):e25050.
PUBMED | CROSSREF
4. Chang MH. Hepatitis B vaccination: disease and cancer prevention-a Taiwanese experience. Clin Liver Dis 2010;14:521-30.
PUBMED | CROSSREF
5. Hsu SC, Chang MH, Ni YH, Hsu HY, Lee CY. Horizontal transmission of hepatitis B virus in children. J Pediatr Gastroenterol Nutr 1993;16:66-9.
PUBMED | CROSSREF
6. Ni YH, Chen DS. Hepatitis B vaccination in children: the Taiwan experience. Pathol Biol (Paris) 2010;58:296-300.
PUBMED | CROSSREF
7. Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev 2006;28:126-35.
PUBMED | CROSSREF
8. Nayagam S, Thursz M. Strategies for global elimination of chronic HBV infection: 2019 update. Curr Hepatol Rep 2019;18:300-9.
CROSSREF
9. Su WJ, Chen SF, Yang CH, Chuang PH, Chang HF, Chang MH. The impact of universal infant hepatitis B immunization on reducing the hepatitis B carrier rate in pregnant women. J Infect Dis 2019;220:1118-26.
PUBMED | CROSSREF
10. Lin CC, Hsieh HS, Huang YJ, Huang YL, Ku MK, Hung HC. Hepatitis B virus infection among pregnant women in Taiwan: comparison between women born in Taiwan and other southeast countries. BMC Public Health 2008;8:49.
PUBMED | CROSSREF
11. 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.
PUBMED | CROSSREF
12. Chen SC, Toy M, Yeh JM, Wang JD, Resch S. Cost-effectiveness of augmenting universal hepatitis B vaccination with immunoglobin treatment. Pediatrics 2013;131:e1135-43.
PUBMED | CROSSREF
13. Hsu HY, Chang MH, Chen DS, Lee CY, Sung JL. Baseline seroepidemiology of hepatitis B virus infection in children in Taipei, 1984: a study just before mass hepatitis B vaccination program in Taiwan. J Med Virol 1986;18:301-7.
PUBMED | CROSSREF
14. Tsen YJ, Chang MH, Hsu HY, Lee CY, Sung JL, Chen DS. Seroprevalence of hepatitis B virus infection in children in Taipei, 1989: five years after a mass hepatitis B vaccination program. J Med Virol 1991;34:96-9.
PUBMED | CROSSREF
15. Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, et al. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in taiwan. JAMA 1996;276:906-8.
PUBMED | CROSSREF
16. Ni YH, Chang MH, Huang LM, Chen HL, Hsu HY, Chiu TY, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. Ann Intern Med 2001;135:796-800.
PUBMED | CROSSREF
17. Ni YH, Huang LM, Chang MH, Yen CJ, Lu CY, You SL, et al. Two decades of universal hepatitis B vaccination in taiwan: impact and implication for future strategies. Gastroenterology 2007;132:1287-93.
PUBMED | CROSSREF
18. Ni YH, Chang MH, Wu JF, Hsu HY, Chen HL, Chen DS. Minimization of hepatitis B infection by a 25-year universal vaccination program. J Hepatol 2012;57:730-5.
PUBMED | CROSSREF

19. Ni YH, Chang MH, Jan CF, Hsu HY, Chen HL, Wu JF, et al. Continuing decrease in hepatitis B virus infection 30 years after initiation of infant vaccination program in Taiwan. Clin Gastroenterol Hepatol 2016;14:1324-30.
PUBMED | CROSSREF

20. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Gevana: World Health Organization, 2016.

21. Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, et al. Humoral and cellular immune responses to a hepatitis B vaccine booster 15-18 years after neonatal immunization. J Infect Dis 2008;197:1419-26.
PUBMED | CROSSREF

22. Chang MH, Lee CY, Chen DS, Hsu HC, Lai MY. Fulminant hepatitis in children in Taiwan: the important role of hepatitis B virus. J Pediatr 1987;111:34-9.
PUBMED | CROSSREF

23. Kao JH, Hsu HM, Shau WY, Chang MH, Chen DS. Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan. J Pediatr 2001;139:349-52.
PUBMED | CROSSREF

24. Chen HL, Chang CJ, Kong MS, Huang FC, Lee HC, Lin CC, et al. Pediatric fulminant hepatic failure in endemic areas of hepatitis B infection: 15 years after universal hepatitis B vaccination. Hepatology 2004;39:58-63.
PUBMED | CROSSREF

25. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA 2013;310:974-6.
PUBMED | CROSSREF

26. Chang MH, Chen DS, Hsu HC, Hsu HY, Lee CY. Maternal transmission of hepatitis B virus in childhood hepatocellular carcinoma. Cancer 1989;64:2377-80.
PUBMED | CROSSREF

27. Chang MH, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC, et al. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. Gastroenterology 2016;151:472-80.e1.
PUBMED | CROSSREF

28. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997;336:1855-9.
PUBMED | CROSSREF

29. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst 2009;101:1348-55.
PUBMED | CROSSREF

30. 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.
PUBMED | CROSSREF

31. Tang JR, Hsu HY, Lin HH, Ni YH, Chang MH. Hepatitis B surface antigenemia at birth: a long-term follow-up study. J Pediatr 1998;133:374-7.
PUBMED | CROSSREF

32. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-99.
PUBMED | CROSSREF

33. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98.
PUBMED | CROSSREF

34. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
PUBMED | CROSSREF

35. Chen HL, Wen WH, Chang MH. Management of pregnant women and children: focusing on preventing mother-to-infant transmission. J Infect Dis 2017;216(suppl_8):S785-91.
PUBMED | CROSSREF

36. Song J, Yang F, Wang S, Tikande S, Deng Y, Tang W, et al. Efficacy and safety of antiviral treatment on blocking the mother-to-child transmission of hepatitis B virus: a meta-analysis. J Viral Hepat 2019;26:397-406.
PUBMED | CROSSREF

37. 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.
PUBMED | CROSSREF

38. 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.
PUBMED | CROSSREF

39. Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med 2018;378:911-23.
PUBMED | CROSSREF

40. Wen WH, Huang CW, Chie WC, Yeung CY, Zhao LL, Lin WT, et al. Quantitative maternal hepatitis B surface antigen predicts maternally transmitted hepatitis B virus infection. Hepatology 2016;64:1451-61.
PUBMED | CROSSREF

41. Chang KC, Chang MH, Lee CN, Chang CH, Wu JF, Ni YH, et al. Decreased neonatal hepatitis B virus (HBV) viremia by maternal tenofovir treatment predicts reduced chronic HBV infection in children born to highly viremic mothers. Aliment Pharmacol Ther 2019;50:306-16.
PUBMED | CROSSREF