Journal of Clinical and Translational Hepatology **2023**
DOI: 10.14218/JCTH.2022.00332

Review Article

Strategies to Prevent Mother-to-child Transmission of Hepatitis B Virus

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Received: 14 July 2022 | **Revised:** 5 October 2022 | **Accepted:** 12 January 2023 | **Published online:** 10 March 2023

Abstract

Mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is the primary cause of chronic HBV infection worldwide. MTCT prevention and antiviral treatment of infected individuals could eliminate this public health burden. Antiviral treatment of hepatitis B surface antigen (HBsAg)-positive pregnant women and immunoprophylaxis with HBV vaccine and hepatitis B immune globulin are the most effective strategies to interfere with MTCT of HBV. However, for worldwide application of those strategies, feasibility, availability, cost, safety, and effectiveness should be considered. Cesarean section and breastfeeding avoidance in hepatitis B e antigen-positive mothers with a high viral load and without antiviral therapy during pregnancy could be an option, but more supporting evidence is needed. HBsAg screening of all pregnant women is recommended when initiating antiviral therapy and immunoprophylaxis for MTCT prevention, except in areas with limited resources. Timely HBV vaccination series administered soon after birth might be the mainstay of prevention. This review aimed to provide a concise update on the effectiveness of available strategies to prevent MTCT of HBV.

Citation of this article: Sintusek P, Wanlapakorn N, Poovorawan Y. Strategies to Prevent Mother-to-child Transmission of Hepatitis B Virus. J Clin Transl Hepatol 2023. doi: 10.14218/JCTH.2022.00332.

Introduction

Hepatitis B virus (HBV) infection is a burden worldwide. Women with chronic HBV infection have an increased risk for mother-to-child transmission (MTCT). Unlike HBV infection with adult onset, children with HBV infection since birth have a small possibility of hepatitis B surface antigen (HBsAg) seroconversion occurring spontaneously or even after treatment. Thus, the children become chronic HBV carriers and can transmit the virus to others. Strategies to prevent MTCT of HBV could break this vicious cycle and contribute to the World Health Organization (WHO) goal to eradicate HBV by 2030.[1] Current MTCT prevention strategies are sustained by strong evidence supporting the hepatitis B vaccination series, particularly starting soon after birth, including passive immunization with hepatitis B immune globulin (HBIG), or treatment with antiviral therapy in infants of hepatitis B e antigen (HBeAg)-positive mothers or mothers with high viral load during the third trimester of pregnancy.[2,3] As alternative options for mothers with high viral load not receiving antiviral therapy, the most recent meta-analysis suggested cesarean section and breastfeeding avoidance to prevent MTCT of HBV.[4,5] However, strategies to minimize MTCT in undeveloped countries, especially in Africa, are challenging, but will be possible with collaboration and support from funding agencies. The provision of birth-dose injections using auto-disable prefillable injection systems that integrate triple elimination of HBV, HIV, and syphilis; education for healthcare providers, and a controlled temperature chain (CTC) system for HBV vaccine, would help to lower MTCT rates in selected areas such as the Sub-Saharan Africa. In countries with a low prevalence of HBV infection, HBV vaccine is administered in combination with other antigens, with the first dose given at 6 weeks of life. HBsAg screening in all pregnant women could be an approach to initiate MTCT prevention. If HBV infection is detected, family screening should be encouraged and therapy should be considered, if indicated.

Epidemiology

In 2015, the WHO estimated that more than 257 million people have chronic HBV infection and that approximately 887,000 of these people will die from cirrhosis and hepatocellular carcinoma.[1] Chronic HBV infection is endemic to Africa and Asia, and these areas account for 70% of chronic HBV infections worldwide. The overall incidence of chronic HBV infection is 3.5%. According to the WHO, the Western Pacific, African, Eastern Mediterranean, South East Asia, European regions, and the Americas have hepatitis B incidence rates of 6.2%, 6.1%, 3.3%, 2.0%, 1.6%, and 0.7%, respectively.[1] In children <5 years of age, the incidence of chronic

Keywords: Mother-to-child transmission; Children; Hepatitis B virus; Vertical transmission; Prevention; Vaccine.

Abbreviations: CTC, controlled temperature chain; EPI, expanded program of immunization; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, mother-to-child transmission; OBI, occult HBV infection; WHO, the World Health Organization.

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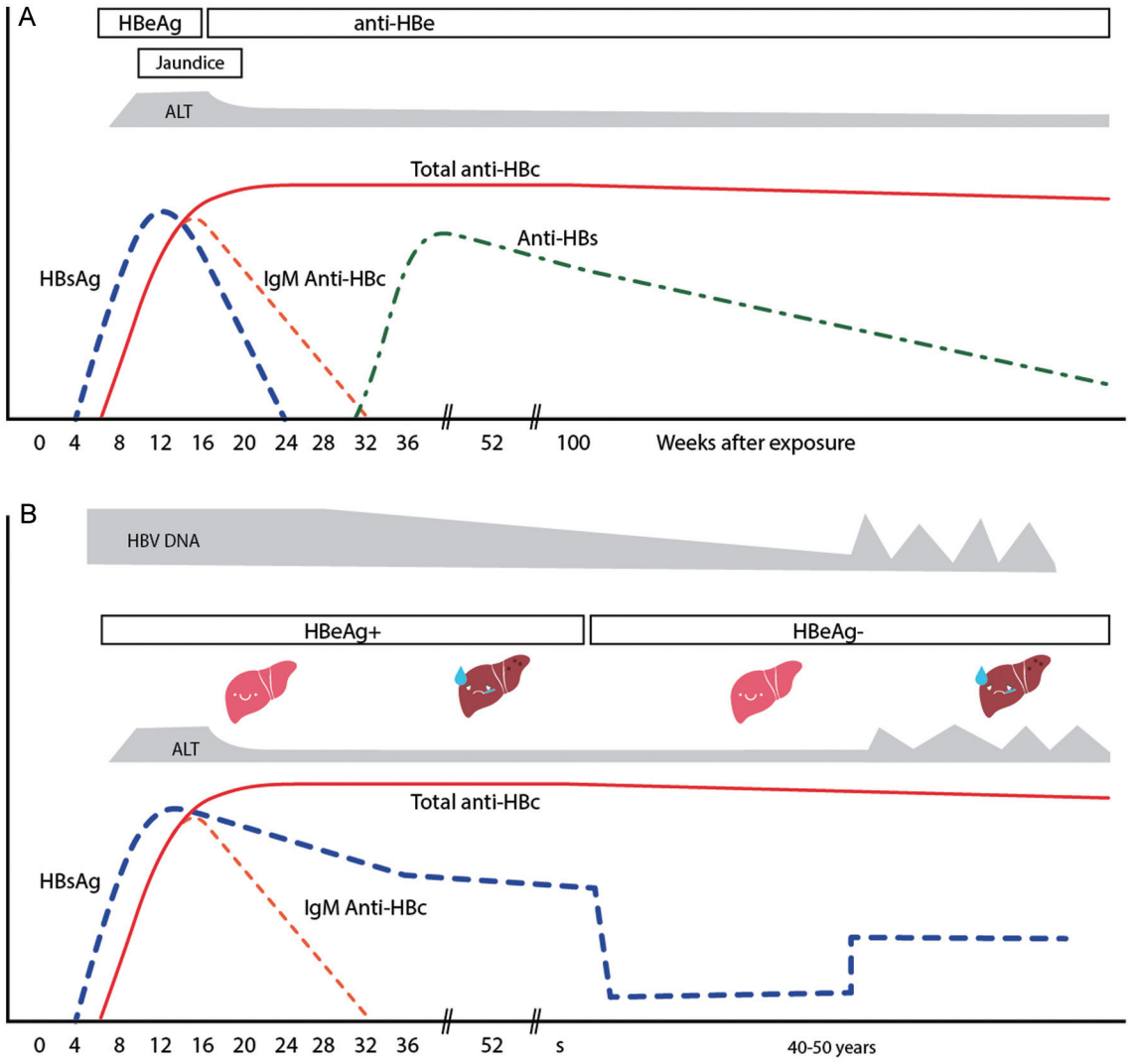

Fig. 1. Natural history of hepatitis B infection. (A) Acute hepatitis B infection. (B) Chronic hepatitis B infection. HBV, hepaitis B virus; HBeAg, hepatitis B. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBc, anti-hepatitis B core; IgM, immunoglobulin M.

HBV has declined to <1% worldwide since the introduction of a safe and inexpensive HBV vaccine in 1981.[6] However, to eradicate HBV, the WHO has set the target as chronic HBV infection incidence of <0.1% in children <5 years age by 2030.[7] For example, Thailand has achieved the WHO target. HBV vaccination was introduced in two provinces in Thailand in 1988 and was expanded to all provinces in 1992 as part of Thailand's expanded program of immunization (EPI).[8] Overall, the rate of HBV infection, most of which involved adults, dramatically decreased from 5.5% in 2004[9] to 1.2% in 2014. Furthermore, the carrier rate among children <5 years of age has been 0.1% since 2014.[10] The success of HBV eradication in Thailand mainly derives from the HBV vaccination series, especially the administration of the first dose at birth.

Viral hepatitis B and pathogenesis

HBV was isolated in 1955[11] from an Australian aborigine and was named the "Australia antigen," which was later identified as the HBsAg. HBV is a small DNA virus that infects humans with the complete hepatitis B virion, known as the Dane particle. The Dane particle is composed of the hepatitis B core antigen (HBcAg) and hepatitis B DNA in the HBsAg envelope. Some Dane particles are composed of HBeAg, which might correlate with high viremia and immune tolerance.[12] HBV may be transmitted to humans vertically from mother-to-child or horizontally via blood transfusion, unprotected sexual intercourse, injection drug use, and rarely from close contact with body fluids.

Natural history of HBV infection and risk of MTCT

In contrast to infection by horizontal transmission in adults, most children with HBV infection by MTCT progress to chronic HBV infection with a lower chance of HBeAg conversion. The natural history of chronic HBV infection is generally divided into four phases (Fig. 1).[13]

HBeAg-positive chronic infection (immune tolerance phase): There is less immune response to HBV during this stage. HBV replicates without any immune reaction, leading to normal liver function tests, high viral load (>2×10^7 IU/mL), high HBsAg level, and HBeAg positivity.

HBeAg-positive chronic hepatitis (immune clear-

ance phase): Upon HBV detection, the immune response to the viral pathogen is activated and the number of viral pathogens decreased (10^4–10^7 IU/mL), leading to liver inflammation. Even with HBeAg positivity and a high HBsAg level, this phase has a high probability of HBeAg seroconversion of up to 90%.

HBeAg-negative chronic infection or inactive carrier (low replication phase): After the immune clearance phase and HBeAg seroconversion, the immune response and viral pathogen load decrease (<2,000 IU/mL) and leads to normal liver function tests. There is a change in HBsAg seroconversion, but the probability of HBsAg loss is only 1–3% in this phase.

HBeAg-negative chronic hepatitis (re-activation phase): The low number of viral pathogen (>2,000 IU/mL) initiates an immune response, and liver inflammation or hepatitis occurs. However, HBsAg seroconversion is very unlikely.

If HBV is transmitted by MTCT, most children with infection remain HBeAg-positive and develop chronic infection or remain in the hepatitis stage until, in case of female infants, they reach reproductive age and become pregnant. These HBeAg-positive pregnant women are likely to have very high serum viral loads and a high possibility of MTCT of HBV. Children of HBeAg-positive mothers have a very high risk of HBV infection, and >90% of those who were not subjected to any prevention strategies will be carriers.[14] On the contrary, children of HBeAg-negative mothers have only a 5–7% chance of contracting an infection, but progress to acute hepatitis and fulminant hepatitis more frequently than those with asymptomatic chronic infection (Fig. 1).[14]

Stages of MTCT of viral hepatitis B and prevention strategies

There are three possible stages of HBV infection by MTCT.

Prenatal transmission (*in utero* transmission): HBV infection by MTCT may occur *in utero* (Fig. 2), which could explain immunoprophylaxis failure. HBV has been detected in the placenta, umbilical cord, and liver tissue of infants who died *in utero*, which implies that HBV infection occurred *in utero*.[15–21] Strategies to prevent HBV infection by MTCT in the prenatal period include early detection by universal HBsAg screening during pregnancy followed by HBeAg screening. HBV DNA/viral load should be evaluated if HBsAg is positive. However, in areas with scant resources, the WHO recommends using HBeAg alone, instead of viral load, as an indicator for initiating antiviral therapy. A systematic review of 27 studies indicated that the sensitivity and specificity of HBeAg for the diagnosis of HBV viremia with a DNA threshold ≥5.3–6.2 $\log_{10}$ IU/mL were 88.2% [95% confidence interval (CI): 83.9–91.5] and 92.6% (95% CI: 90–94.5), respectively.[1] To assess maternal health, women should be referred to specialists for disease evaluation and proper treatment following international guidelines.[22,23]

Invasive obstetric procedures during pregnancy increase the risk of HBV infection by MTCT (Fig. 2) and should be initially carefully considered in pregnant women who was positive in HBeAg screening.[24] In a recent case–control study, the risk of MTCT of HBV was significantly higher in women with a high HBV DNA viral load (≥7 $\log_{10}$ copies/mL) who underwent amniocentesis than in those who did not (50% vs. 4.5%; odds ratio: 21.3; 95% CI: 2.96–153.77).[25]

Perinatal transmission: Most HBV infections by MTCT occur at birth, and studies have demonstrated the presence of viral pathogen in the placenta, umbilical cord, gastric content, amniotic fluid, and vaginal fluid, and very high viral loads in infant serum during the first 2–3 months of life.[26] Complications of labor, including threatened preterm labor and threatened abortion, and history of MTCT in a previous pregnancy might increase the risk for MTCT.[27] In cases of preterm labor, there is no evidence of a high rate of MTCT in preterm infants.[15,28,29] Still, theoretically, these infants may be potentially exposed to infection by procedures that cause breaks in the skin or mucosal barrier (Fig. 2), such as fetal scalp blood sampling or vigorous suction after birth.[27]

There is a hypothesis that high maternal viral load associated with HBeAg positivity may result in a risk of infection in the perinatal stage. Lowering the viral burden during pregnancy could prevent HBV infection by MTCT at this stage. Most studies,[30–32] including a systematic review,[33] reported the effectiveness of antiviral therapy such as telbivudine, tenofovir, or lamivudine during the late stage of pregnancy compared with immunoprophylaxis alone in HBeAg-positive pregnant women with high viral loads without any severe side effects. Consequently, most national and international guidelines recommend antiviral therapy if the HBV DNA level is higher than the established threshold using telbivudine, tenofovir, or lamivudine during the third trimester. However, in 2018, Jourdain *et al*.[34] conducted a randomized controlled trial study in Thailand to compare antiviral therapy (tenofovir) with immunoprophylaxis or immunoprophylaxis alone in HBeAg-positive mothers. They found no significant difference in the MTCT rates between the two groups. To our knowledge, that is the only RCT that questioned the efficacy of antiviral therapy to prevent MTCT. Another protective factor was the very early treatment with a birth dose at <3 h of life in the the study participants, which might be the reason for the high effectiveness of immunoprophylaxis.

Theoretically, passive immunity from HBIGs would prevent MTCT during labor. As HBV infection has a long incubation period, active immunity through HBV vaccination could prevent infection if given as soon as possible. As a result, immunoprophylaxis initiated in this stage has a high-cost effectiveness.[35–37] At birth, the mainstay of prevention is active immunoprophylaxis with a series of at least three doses of HBV vaccine, as the timely birth dose within 12 to 24 h after birth.[7,38,39] Passive immunoprophylaxis using HBIGs is recommended to increase the success rate of MTCT if given within 12 to 24 h.[7,39] However, HBIG is not readily available in countries with scant resources given the requirement for the cold chain process, inadequate supplies, and high costs. Recent studies, including a systematic review, have demonstrated no significant difference in treatment with vaccine alone or in combination with HBIG to prevent HBV MTCT,[40] especially in HBeAg-negative mothers.[41] Poovorawan *et al*.[39] found that in countries with limited HBIG resources, such as Thailand, a timely birth dose of HBV vaccine within 12 h of birth without HBIG or antiviral therapy during pregnancy could prevent MTCT, in which only 2 of 55 children were born HBV-positive, which implied an efficacy of up to 96%. Poovorawan *et al.*[42] also compared infants who received an HBV vaccination series at birth, 1 month, and 6 months of life with HBIG and a HBV vaccine series alone. They reported a protective efficacy of 94.8% in infants receiving HBV vaccination series alone and 100% in infants receiving both HBV vaccination series and HBIG administration at birth. In Thailand, the protective efficacy of a birth dose of HBV vaccine, usually given at <3 h after birth, either alone or combined with HBIG, was very high. The very high protective efficacy of timely birth dose of HBV vaccination combined with HBIG might explain why antiviral therapy in HBeAg-positive mothers had no additional protective efficacy from HBV vaccination series combined with HBIG. A very prompt HBV vaccine birth dose within 12 h (usually <3 h) after birth might be an

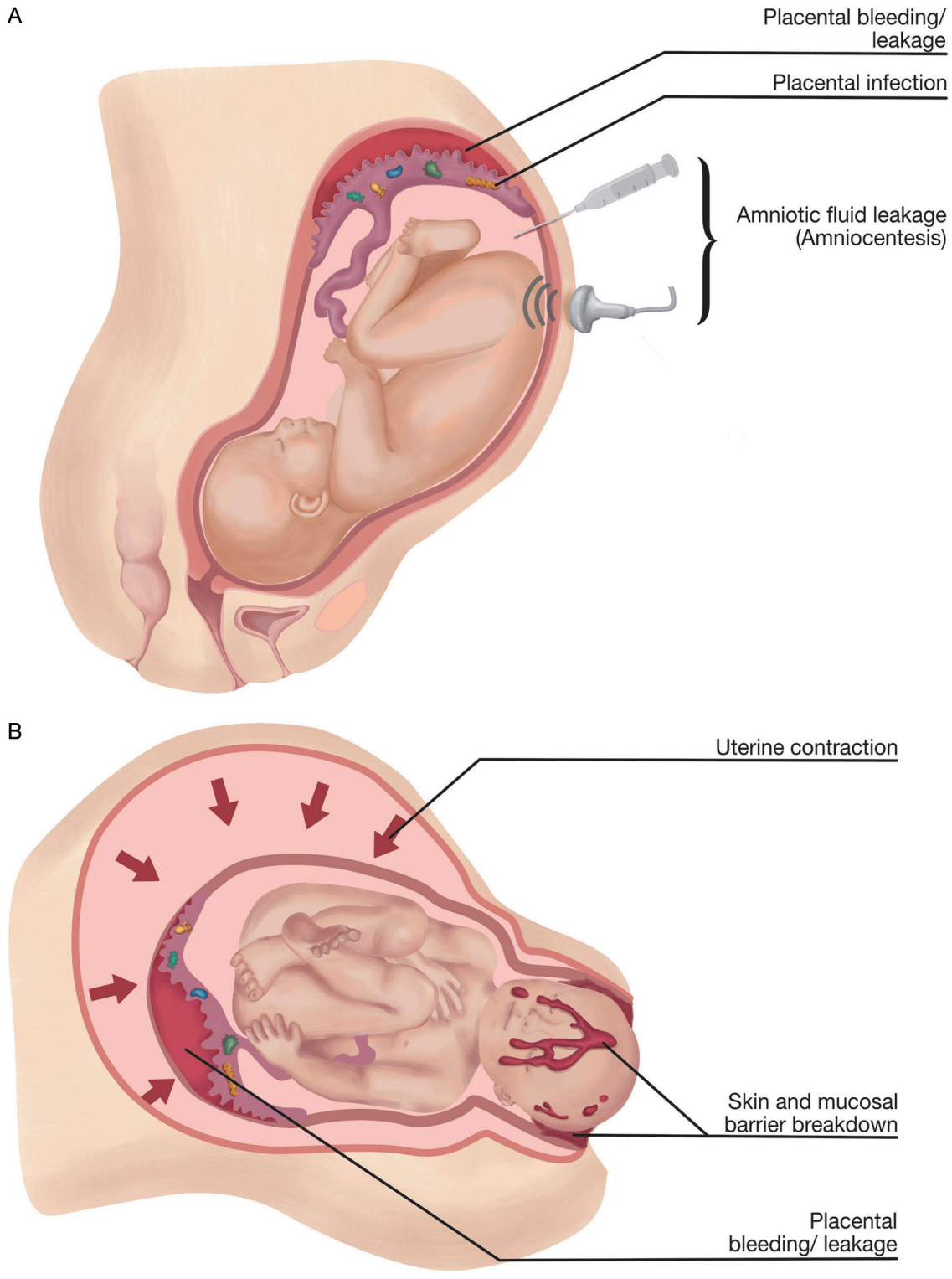

Fig. 2. Illustrations of the possible mechanisms of vertical transmission. (A) Prenatal period, (B) Perinatal period.

additional and simple strategy to increase the success rate of MTCT prevention. Further study investigating the efficacy of HBV vaccination alone within hours of birth is warranted, especially in undeveloped countries such as Sub-Saharan Africa where HBIG is less accessible.

Despite the low occurrence of HBsAg, a high frequency of transient occult HBV infection (OBI), defined by HBV DNA positivity but anti-HBcAg and HBsAg negativity at 1 year of

age, was reported in 8.3–9.9% of immunized infants born to HBsAg-positive mothers.[43] A recent study reported OBI in 6.8% of children (3/44) born to HBsAg-positive mothers. One in three children progressed to overt HBV infection or seropositivity for HBsAg and anti-HBcAg after 5–7 years of follow-up.[44] However, the rapid administration of a timely HBV birth dose might be effective in preventing OBI. Lu *et al.*[45] found that a birth dose administered within 6 h significantly reduced OBI occurrence at the 36-month follow-up. Therefore, a timely birth dose with a HBV vaccination series not only prevented overt infection but also reduced OBI occurrence. However, long-term follow-up and close monitoring of children with OBI is needed, as there might be an increased risk of overt HBV infection under these circumstances.[46,47] Other OBI-associated factors and their clinical importance should be further investigated. Rarely, virological factors that could lead to immunoprophylaxis failure involve a viral escape mutant.[48]

A genetic analysis of a determinant in HBsAg might have a role. Interestingly, a recent systematic review study demonstrated the increased risk of MTCT from natural labor compared with cesarean section in HBeAg-positive mothers with high viral loads.[4] The findings conflict with the recommendations of all the currently available guidelines[1,3,49] that favor cesarean section or instrument assisted-delivery over obstetric indications such as labor dystocia, abnormal or indeterminate fetal heart rate tracing, previous cesarean section, breech presentation, HIV-positive pregnant woman with high viral loads, etc. However, there were the critical comments about the methodology of this meta-analysis study, especially the inclusion/exclusion of some studies,[5,50] possible misrepresentation of a study, and merging data of urgent cesarean section into the vaginal delivery group, instead of merging data of urgent cesarean section into elective cesarean section before the analysis.[5] Moreover, the cost–benefit and safety of elective cesarean section should be further evaluated before applying this strategy for MTCT prevention in all HBeAg-positive mothers with high viral load.

Postnatal transmission: Although HBV DNA can be detected in maternal breast milk and saliva, the viral load is very low compared with levels in the blood. Thus, most studies have found that breastfeeding and close contact did not appear to significantly increase the risk of MTCT.[1,2,13,26,51] However, a systematic review and meta-analysis by Pan *et al.*[4] showed that a non-breastfeeding modality had a significantly reduced risk of MTCT in HBeAg-positive mothers with high viral loads who did not receive antiviral therapy during pregnancy. From that study, the possibility of MTCT in breastfeeding might be attributed to the presence of cracked nipples or lesions of the infant skin that might have acted as the major route of HBV transmission via the bloodstream, not via breast milk. Unfortunately, no discussion exists about this crucial aspect on that meta-analysis study.[4] Thus, we recommend continuing breastfeeding in mothers who received antiviral agents (tenofovir, lamivudine, or telbuvudine) in the third trimester of pregnancy. In mothers who do not receive an antiviral agent to lower the HBV viral load during pregnancy, breastfeeding should be postponed if they have cracked nipples, which would allow the virus to infect their infants via the bloodstream.

In addition, given its availability and cost effectiveness, active immunoprophylaxis is the mainstay of preventing MTCT. An HBV vaccination series is effective if administered at birth, 1 month, and 6 months of age.[42] However, the schedule for the HBV vaccination series in Thailand differs from that in other countries, with 4–5 doses of HBV vaccine indicated by Thailand's EPI. The policy is based on a study by Poovorawan *et al*.,[52] which compared two regimens of HBV vaccination given at birth and at 2, 4, and 6 months versus HBV vaccine given at birth and at 1, 2, 4, and 6 months. They found a significantly improved effectiveness with five doses of HBV vaccine to prevent HBV infection in HBsAg-positive mothers. The study underlined the protective efficacy of a timely birth dose and multiple injections, especially if there were no delays in the second dose. As the rate of HBV vaccination failure in infants with HBsAg-positive mothers is very low even without antiviral therapy during pregnancy,[34,42] we hypothesize that a robust active immunity resulted from the very prompt administration of a HBV vaccine birth dose (usually within 3 h of birth)[34] and multiple HBV vaccination series in these high-risk infants might be another additional factor in reducing the risk of MTCT. In particular circumstances, such as preterm infants with body weights of <2,000 g, an additional dose should be administered, that is vaccinations at birth, body weight >2,000 gm, and 1, 2, 4, and 6 months of age.

Evaluation of HBV infection in infants born to hepatitis B-positive mothers

The WHO recommends HBsAg and anti-HBs testing at least 1 month after the HBV vaccination series or at 7–12 months of life to evaluate the effectiveness of the strategy to prevent hepatitis B MTCT and identify infants with potential HBV infection.[1] Nevertheless, passive maternal anti-HBcAg can be transferred to an infant and detected in serum for up to 12–18 months. Infants with suspected HBV infection (negative HBsAg and anti-HBcAg) should be tested at 12–18 months of age. Anti-HBcAg levels >10 mIU/mL are considered to have induced immune protection, whereas revaccination for HBV and evaluation of HBV DNA are necessary to rule out OBI in children with anti-HBcAg levels <10 mIU/mL.

Summary of recommendations from current guidelines to prevent HBV MTCT infection and recent evidence

International guidelines for MTCT prevention vary based on the available evidence, HBV distribution, cost effectiveness, and year of the published recommendation. Guidelines of the WHO,[1] American Association for the Study Liver Disease,[2] European Association for the Study of Liver,[13] and the Asian Pacific Association for the Study of Liver[49] recommend antiviral prophylaxis at the third trimester of gestation in combination with immunoprophylaxis with HBV vaccine in HBeAg-positive pregnant woman with high viral load, and HBIG at birth, and the HBV vaccination series to prevent MTCT. The guidelines relative to the delivery mode and infant feeding should be clarified, as they conflict with the results of a recent systematic review.[4] However, generalizing a specific strategy appropriate for different countries or situations is challenging. Making decisions based on site-specific studies is difficult, and patient management should consider making decisions on a case-by-case basis.

Studies of the efficacy, cost effectiveness, and risk–benefit of different management options and results of more recent studies published after the available guidelines should be further evaluated before their routine application in clinical practice worldwide (Table 1). Nakayam *et al*.[1,2,4,7,14,30,46] suggested using a compact prefilled auto-disposable device and CTC system to avoid the cold chain requirement for HBV vaccine storage so that the HBV vaccine could be administered promptly to infants even in out-of-hospital birth situations, which are significant barriers in Sub-Saharan Africa. In contrast with the European region, where there is a very low prevalence of HBV infection, strategies for appropriate

Table 1. Summary of recommendations from international guidelines and the most recent systematic review study

Guidelines	WHO[1] (2020)	APASL[46] (2015)	AASLD[2] (2018)	EASL[14] (2017)	This review
Antivirals	Tenofovir (low genetic barrier and side effect)	Tenofovir or telbivudine	Tenofovir, telbivudine or lamivudine	Tenofovir	Tenofovir, telbivudine or lamivudine[30]
HBV VL threshold to start antivirals	>2×10^5 IU/mL or HBeAg positive where HBV DNA testing is not available	>2×10^6 IU/mL	>2×10^5 IU/mL	>2×10^5 IU/mL or HBsAg; >4 log10 IU/mL	HBeAg testing as an alternative measure to identify mother with high VL[1]
Initiation and cessation of antivirals	28 weeks until at least birth	28–32 weeks until delivery	28–32 weeks until 3 months after delivery	24–28 weeks until up to 3 months after delivery	
Mode of delivery	No difference	No difference	No difference	No difference	Cesarean section in HBeAg-positive mother who not receive antiviral therapy
Hepatitis B vaccine series	≤24 h and follow with at least 2–3 doses	≤24 h	≤12 h	≤12 h	< 3 hr in mother with high VL
HBIG	Recommended if HBeAg-positive mothers	Recommended if HBeAg-positive mothers	Not contrary	Recommended	–
Breastfeeding	Recommend	Recommended	Recommended	Recommended	Not recommend in mother with high VL[4]
Breastfeeding if mother continues antiviral drug	Not against	Not recommended	Not against	Not against	–

WHO, the World Health Organization; APASL, the Asian Pacific Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; VL, viral load; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin.

testing and treatment during the perinatal period could be considered more feasible during the current EPI for HBV.

Proposed strategies for MTCT from the available guidelines and recent evidence-based studies

To reduce the incidence of MTCT to <0.1% worldwide by 2030, as proposed by the WHO, more accessible and flexible strategies should be adopted based on strong supporting evidence. Collaboration and empowerment among authorities, government bodies, healthcare workers, and patients should be integrated. The proposed plans to prevent MTCT are shown in Figure 3.

Conclusions

As the WHO has endorsed a Global Health Sector Strategy to eliminate viral hepatitis by 2030, many studies have investigated prevention strategies for HBV infection by MTCT to break the cycle of chronic HBV infection in future generations. Strategies that have been demonstrated to be very effective and could be used worldwide include active immunoprophylaxis with HBV vaccine as soon as possible after birth (<3 h), followed by HBV vaccination series of at least two doses. Other highly effective strategies, although more challenging to generalize worldwide, include HBIG administration within 12–24 h after birth and perinatal prevention with antiviral agents during the third trimester of gestation in HBeAg-positive pregnant woman. The most recent systematic review from China reported a significantly lower risk of MTCT following cesarean section and breastfeeding avoidance for HBeAg-positive mothers not receiving antiviral prophylaxis. Although all these strategies are effective, cost and safety should be considered, with suitable adaptations in patient management on a case-by-case basis for areas with limited resources. Further site-specific research, especially in areas with poor resource availability, is warranted.

Acknowledgments

The authors are very grateful to Miss Alisara Pittiyayon at Electricity Generating Authority of Thailand for the image in Figure 2.

Funding

The work was supported by a grant from Thai Pediatric Gastroenterology, Hepatology and Immunology (TPGHAI) Research Unit, Chulalongkorn University, Bangkok, 10330, Thailand.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (PS, YP), manuscript writing (PS), and critical revision of the manuscript for important intellectual content (NW, YP). All authors have significantly contributed to this study and have approved the final manuscript.

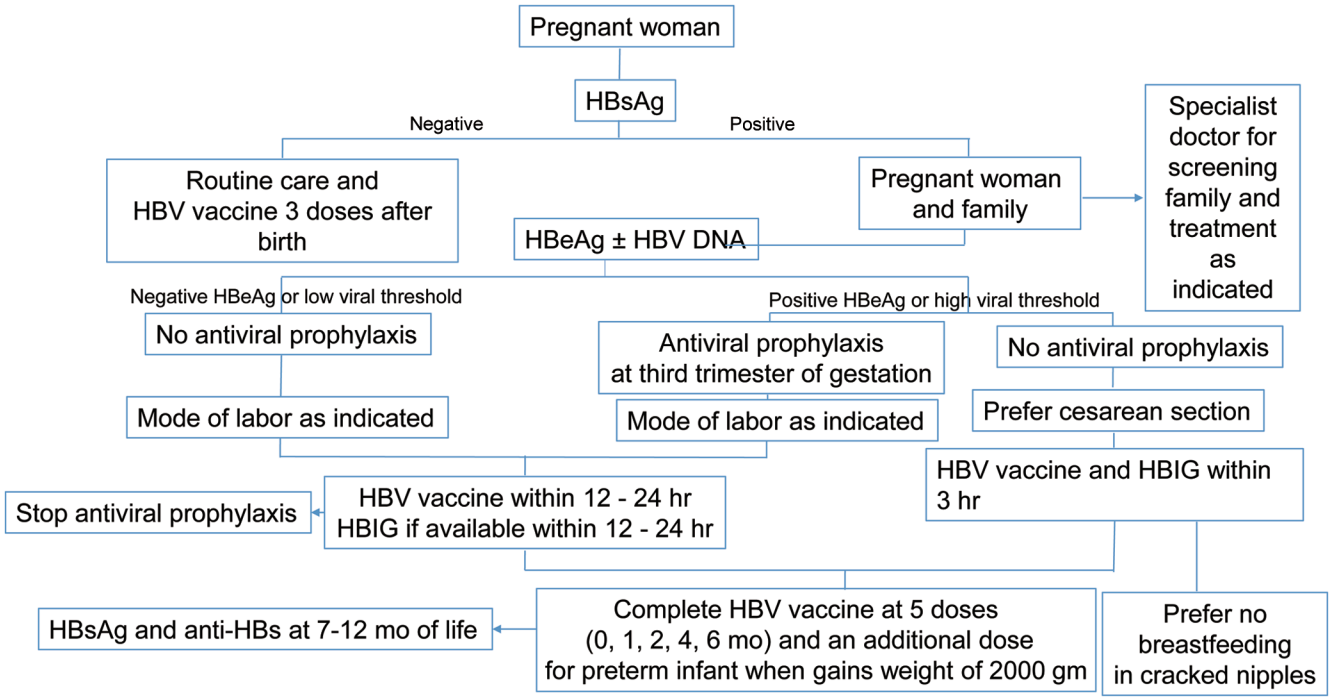

Fig. 3. Algorithm for prevention of hepatitis B virus (HBV) infection by mother-to-child transmission (MTCT). HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; hr, hour; HBIG, hepatitis B immunoglobulin; mo, month.

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