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REVIEW

Exploring the impact of hepatitis B immunoglobulin and antiviral interventions to reduce vertical transmission of hepatitis B virus

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Abstract

Hepatitis B virus (HBV) infection is a major public health burden. In HBV endemic regions, high prevalence is also correlated with the infections acquired in infancy through perinatal transmission or early childhood exposure to HBV, the so-called mother-to-child transmission (MTCT). Children who are infected with HBV at a young age are at higher risk of developing chronic HBV infection than those infected as adults, which may lead to worse clinical outcome. To reduce the incidence of HBV MTCT, several interventions for the infants or the mothers, or both, are already carried out. This review explores the newest information and approaches available in literature regarding HBV MTCT prevalence and its challenges, especially in high HBV endemic countries. This covers HBV screening in pregnant women, prenatal intervention, infant immunoprophylaxis, and post-vaccination serological testing for children.

Key Words: Hepatitis B virus; Hepatitis B immunoglobulin; Mother-to-child transmission; Vertical transmission; Antiviral prophylaxis

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Core Tip: Mother-to-child transmission (MTCT) of the hepatitis B virus (HBV) is still a problem in HBV endemic countries. This review explores the newest information and approaches available in literature to overcome MTCT and its challenges, including screening of pregnant women, prenatal intervention, infant immunoprophylaxis, and post-vaccination serological testing.

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INTRODUCTION

Hepatitis B virus (HBV) infection continues to be a leading cause of morbidity and mortality worldwide. HBV infection causes a wide range of disease manifestations and clinical outcomes from acute asymptomatic to chronic hepatitis B (CHB). Despite the availability of safe and effective vaccines to control viral transmission, more than two billion people in the world are estimated to be affected by HBV infection[1]. CHB leads to long-term inflammation and liver damage that can progress to serious liver diseases, including liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[2]. Currently, over 292 million people globally are chronically infected with hepatitis B. Additionally, an estimated 58 million people have occult hepatitis B infection (OBI). Thus, CHB causes significant health problems, leading to over 880000 deaths annually from cirrhosis and HCC[3].

CHB is estimated to affect 4.1% of people worldwide across all age groups. CHB prevalence varies notably in different regions according to the Global Burden Disease Study 2019[4]. In Africa, the HBV infection rate is particularly high, with an estimated 6.5% of the population affected. The Eastern Mediterranean and Southeast Asia regions also face a considerable challenge, with 3.1% of its population living with CHB. In the European and Americas regions, the prevalence is relatively lower at 1.1% and 1.2%, respectively[4].

As the Asia-Pacific region is home to more than half of the global population, it has the highest number of deaths due to HBV. CHB was a major cause of death from cirrhosis in the Asia-Pacific region in 2015. Also, in that year, more than two-thirds of all cases of acute viral hepatitis in the world occurred in this region[5]. Most of the burden of HBV-related diseases in the Asia-Pacific region is mainly due to the infections acquired in infancy *via* perinatal transmission or early childhood exposure. Children who are infected with HBV at a young age are much more likely to develop CHB than adults. The risk of CHB infection is highest in infants who are infected in the first year of life (80%–90%) compared to children infected between 1 and 5 years of age (30%–50%) and people who are infected as adults (< 5%)[6,7].

There are limited accurate and large-scale data on the prevalence of hepatitis B surface antigen (HBsAg) in pregnant females in the Asia-Pacific region[7]. Varying rates of HBsAg positivity in pregnant women have been reported, from 0.1%–1.0% in Japan, 3% in South Korea, 4% in Mongolia, and up to 6% in China. In the Western Pacific region, perinatal transmission is estimated to cause 180000 new HBV infections in infants each year[8]. A study in Indonesia found that 2.76% of almost 70000 pregnant women across 12 provinces had HBV infection in 2015. Prevalence was found to be lowest in West Sumatra (1.6%) and highest in West Papua (8.0%)[9]. In addition, a study of pregnant women conducted in 37 midwifery clinics and one private obstetric clinic from July 2018 to April 2019 in Bandung, West Java, Indonesia found that 6.1% were HBsAg seropositive[10]. A review of studies conducted across Southeast Asia and the Western Pacific regions between 1983 and 2016 found that the prevalence of HBsAg in children born to mothers who were also hepatitis B e antigen (HBeAg) seropositive ranged from 2.7% to 53.0%[11].

Managing hepatitis B in pregnant women requires careful consideration for both the mother's health and the risk of viral transmission to the infant. The World Health Organization (WHO) has established global targets to eliminate viral hepatitis as a significant public health threat by 2030. These goals include: (1) Reduction of new chronic HBV infections by 90% (which means less than 0.1% of 5-year-olds with HBsAg seropositive); (2) Increase the coverage of the hepatitis B vaccine birth-dose (HepB-BD) within 24 hours of birth (to protect the newborns) by 90%; and (3) Increase coverage of the third dose HepB in infants by 90%[12].

HBV VERTICAL TRANSMISSION ROUTE

Mother-to-child transmission (MTCT) of HBV involves the transfer and reproduction of HBV from the mother to the child, resulting in the generation of new viral particles[7]. HBV vertical transmission is defined as the transfer of infection from mother to child either during pregnancy, childbirth, or after delivery[1], as depicted in Figure 1.

While the specific prevalence of transmission routes remains uncertain, delivery-related transmission appears to be the primary cause of vertical transmission. Notably, the presence of HBeAg and high HBV DNA viral load (VL) in mothers are significant risk factors for mother-to-infant transmission[13]. Following the availability of hepatitis B immunoglobulin (HBIG) and effective HepB, the rates of MTCT in children born to mothers with CHB, whether they are HBeAg seropositive or seronegative, have decreased dramatically to approximately 4%–10% and less than 0.1%, respectively[14,15].

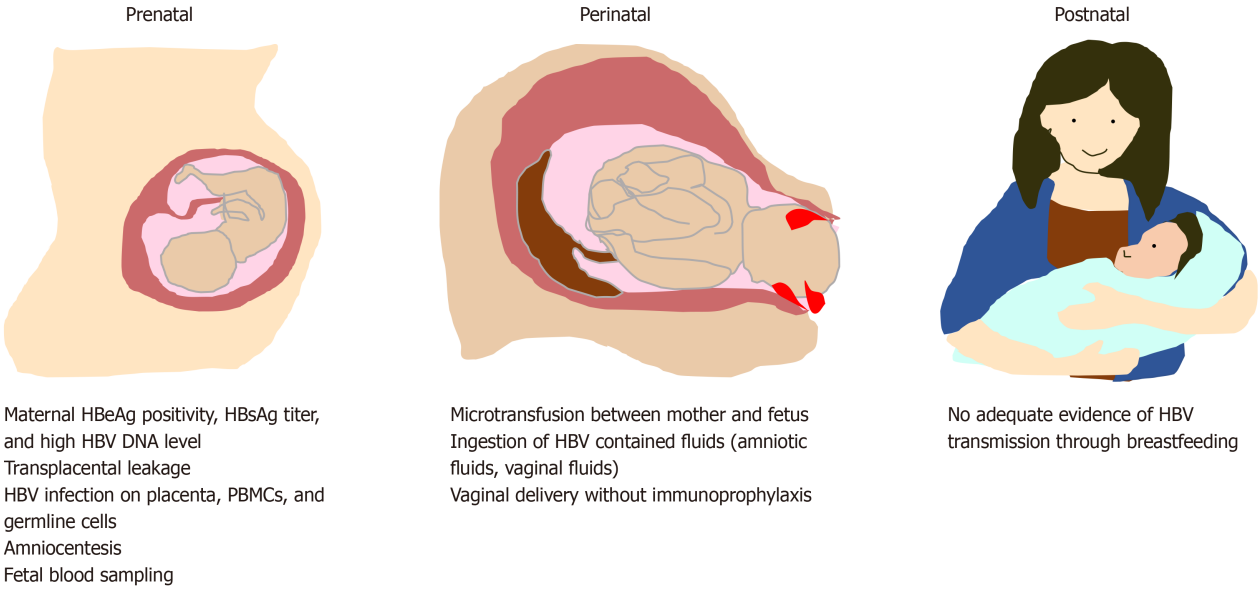

Figure 1 Modes of mother-to-child transmission of hepatitis B virus. HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

Prenatal transmission

HBV transmission during pregnancy refers to intrauterine transmission. The risk factors for HBV intrauterine transmission are still poorly understood. Various reports have identified potential factors associated with intrauterine transmission of HBV including method of delivery, prior abortion history, antepartum hemorrhage, and maternal HBV DNA load, although with conflicting results[16-18]. The intrauterine HBV infection rate was found to be linear with maternal serum HBsAg titers and HBV DNA concentrations[17]. There are several mechanisms that would allow for intrauterine HBV transmission, these include viral infection of the placenta, maternal HBeAg positivity, extrahepatic reservoirs, transplacental leakage and the impact of medical procedures[19,20].

Viral infection of the placenta

The placenta typically protects against the transmission of blood-borne pathogens to the fetus. However, several studies have reported the presence of HBV particles, HBsAg, and HBV DNA, in the four distinct layers of the placenta, with varying rates of HBV infection among the different layers[21]. The rate of HBV infection diminishes gradually within the maternal-to-fetal placental layer, with HBV detection rate in decidua cells, trophoblastic cells, villous mesenchymal cells, and villous capillary endothelial cells 55.4%, 51.0%, 46.5%, and 29.9%, respectively[21]. HBV was also present in both the endothelial cells of the villous capillaries and the trophoblasts within the placenta, supporting the theory that a breach of the placental barrier as one of the pathways for intrauterine infection[17,22]. Thus, HBV has the potential to breach the placental barrier, leading to viral infection and replication across various types of placental cells prior to reaching the fetus[23]. The rates of HBV infection in the placenta increase with the stage of pregnancy. The HBV infection rates during the first trimester, second trimester, and full-term were found to be 4.2%, 16.6%, and 44.6%, respectively[24].

Maternal HBeAg positivity

More recent research has identified maternal HBeAg positivity and high HBV DNA VL as the most critical risk factors for HBV vertical transmission. In a study by Xu *et al*[17], maternal HBeAg positivity, HBsAg titer, and HBV DNA level were observed to be risk factors for transplacental HBV transmission[17]. A more recent study has also shown that the placental infection rate was higher in HBeAg-positive mothers compared to the HBeAg-negative group [odds ratio (OR) = 15.56, 95%CI: 2.5-95.7], in addition, placental infection was significantly related to intrauterine transmission of HBV (OR = 4.6, 95%CI: 2.29-9.4)[25]. Thus, HBeAg positivity in mothers might indicate increased intrauterine transmission risks for the infant. However, Chalid *et al*[26] noted a 3.1% occurrence of high HBV DNA level (> 5.3 Log_{10} copies/mL) in the cord blood of HBeAg seronegative mothers, indicating the limited effectiveness of HBeAg detection in predicting intrauterine transmission[26]. Thus, relying solely on HBeAg status to predict intrauterine transmission may not be sufficient. Other factors, such as HBV DNA levels and placental infection rates, also play a crucial role in transmission risk, indicating the need for a more comprehensive approach to assess and manage HBV transmission risk during pregnancy.

Extrahepatic reservoirs

Extrahepatic reservoirs and germline infections also increase the risk of HBV prenatal transmission. Peripheral blood mononuclear cells (PBMCs) might serve as extrahepatic reservoirs as HBV DNA has been detected in these cells. A 2015 study showed that infants born to mothers with HBV DNA-seronegative but HBV DNA-positive PBMCs have a 5-fold higher risk of HBV infection compared to those born to mothers with HBV DNA-negative PBMCs[27]. HBV presence in germline cells has also been demonstrated[20]. In male CHB patients, HBV may be present as either free viral particles in the seminal plasma or as integrated DNA in the genome of spermatozoa[28]. This HBV presence has been associated with

adverse effects on the motility and fertilizing abilities of sperm and may even induce chromosomal aberrations during embryo development due to the high incidence of integrated viral DNA[29]. In female CHB patients, HBV has been shown to infect the ovum at different stages of development and may even replicate within the ovum[30]. HBV expression in the oocyte has been associated with HBV DNA level and infection status of the mother[31]. Despite all these findings, there is still limited understanding on whether HBV-infected germlines from the parent can be passed directly to the infant.

Transplacental leakage and the impact of medical procedures

Transplacental leakage may occur when the placental barriers are ruptured, which allows for direct exchange between the fetal and maternal blood. This might occur in early pregnancy due to immaturity of the placenta. The transfer of HBeAg-positive maternal blood across the placenta, which can be triggered by uterine contractions during pregnancy or disruptions in placental barriers (such as threatened preterm labor or spontaneous abortion), is a probable pathway for HBV intrauterine infection.

Invasive medical procedures, such as amniocentesis and chorionic sampling during pregnancy have also been reported to increase the risk of HBV prenatal transmission[20]. Amniocentesis has been shown to significantly increase the rate of MTCT (OR = 21.3, 95%CI: 2.90-153.775) on studies in HBsAg- and HBeAg-positive mothers with a very high HBV DNA level (≥ 7 Log_{10} copies/mL)[32]. Needle penetration during amniocentesis can damage chorionic villi, leading to the mixing of maternal and fetal blood, and may cause bleeding from fetal-maternal capillaries within the fetal membranes [23]. These studies indicated that in pregnant mothers with high HBV DNA VL, amniocentesis procedures should not be encouraged or only be considered after proper risk and benefit assessment to reduce viral transmission rate to the infant [19,33].

A recent case report assessing the impact of fetal blood sampling during pregnancy on MTCT rate showed that, like amniocentesis, fetal blood sampling in HBsAg-positive women also increased the risk of MTCT. Performing fetal blood sampling for prenatal diagnosis prior to postnatal immunoprophylaxis can heighten the likelihood of intrauterine HBV infection due to potential placental disruption and maternal blood contamination[34,35]. This was evident by persistent HBsAg positivity up to 12 months in the infants born to untreated, HBeAg-positive, and high HBV DNA VL mothers. In addition, the infants born to antiviral-treated, HBeAg-positive, and high HBV DNA VL mothers were HBsAg seronegative with antibody to HBsAg (anti-HBs) seropositive status until the end of the follow-up period[36]. More studies are warranted to verify these findings as the study included a very low sample size.

Perinatal transmission

Infection during childbirth may arise due to micro transfusion between the mother and fetus or ingestion of infectious fluid[37]. A previous study showed the presence of HBsAg in a significant proportion in both vaginal epithelial cells (55%–98%) and cervicovaginal cells (12%), along with detectable HBV DNA[38]. Moreover, HBsAg was detected in amniotic fluid samples (26%) and vaginal fluid samples (96%)[39]. These findings suggest that direct exposure to infective fluids in the maternal genital tract could be a possible route of HBV transmission to infants[38,39].

Several studies have explored the impact of delivery mode on HBV transmission risk. Findings from a 1988 study in China showed that among 447 infants born to HBsAg-positive women, around 25% of those delivered vaginally were infected with HBV at birth, compared to less than 10% of those delivered *via* cesarean section[40]. However, a later study found that the incidence of CHB among infants who were born by spontaneous vaginal delivery, either with the use of forceps or vacuum extraction, and by cesarean section and who had received HBIG and HepB vaccination did not differ significantly, at 7.3%, 7.7%, and 6.8%, respectively. These findings indicate that the cesarean section mode of delivery was not sufficient to decrease the MTCT rate, particularly during the occurrence of possible immune prophylaxis failure[16]. However, performing elective cesarean sections for HBeAg seropositive mothers with pre-delivery HBV DNA levels of ≥ 6 Log_{10} copies/mL might decrease the risk of viral transmission from mother to child[41].

Post-natal transmission

In late 1980s, Wong *et al*[39] first reported that breastfeeding poses a significant concern for postpartum HBV transmission, with HBsAg detected in 72% of breast milk samples[39]. However, a more recent study by Chen *et al*[42] suggests that while HBsAg, HBeAg, and HBV DNA are present in both colostrum and breast milk, there is no concrete evidence that breastfeeding increases the risk of HBV MCTC. Their study also found that the prevalence of HBsAg in breastfed infants was 1.5%, compared to 4.7% in formula-fed infants, with no significant statistical difference[42]. These findings suggest that the risk of viral transmission *via* breast milk is minimal, compared to the risk posed by direct exposure to maternal blood or fluids during delivery. Several hepatitis experts have also evaluated the potential danger posed by a significant daily intake of breast milk for the infant, given the delicate condition of the gastrointestinal mucosa and the incomplete development of the digestive tract[43]. However, to date, there is no evidence to show an elevated risk of viral transmission through direct contact with bleeding nipples or open sores on the breast, especially when appropriate immunoprophylaxis has been administered at birth[33,44,45].

CURRENT STRATEGIES TO REDUCE MTCT RATE

The strategy for MTCT elimination differs between different geographical regions, thus, it is important to understand the specific circumstances in each region to find solutions in the local context to eliminate HBV infection[46,47]. Different strategies may be adopted to reduce and prevent the risk of HBV MTCT. These approaches may include targeted in-

tervention only for the infants or the mothers. However, concerted actions for both the infants and the mothers are believed to be more effective in reducing the vertical viral transmission rate. There are four general approaches that need to be included in any HBV MTCT prevention program, especially in high HBV endemic countries: (1) Screening of pregnant women; (2) Prenatal intervention in pregnant women; (3) Timely infant immunoprophylaxis, and (4) Post-vaccination serological testing (PVST) for children[46,47].

Screening of pregnant women

Screening for HBV infection during pregnancy is necessary to identify mothers whose infants are at risk of perinatal transmission. Detection of HBsAg has been demonstrated to be an economical approach and easily applicable even in areas with limited resources. Indeed, HBsAg detection by qualitative rapid detection tests is commonly used for HBV screening programs in pregnant women in Asia and Africa[48-50]. Detection of HBV DNA VL, by quantitative PCR assay, however, can provide a more accurate picture of the maternal HBV infection status. In addition, HBV DNA VL can also be used to identify which mothers need antiviral prophylaxis as high maternal HBV DNA level has been identified as a significant risk factor for HBV MTCT[51,52].

As HBV DNA VL quantification is more costly and requires a proper instrument set-up, use of this method is inefficient particularly in areas with few resources, thus not many HBV screening programs recommend its use[53]. Alternatively, the detection of other HBV serological markers, such as HBeAg and quantitative HBsAg levels, has been identified as possible surrogate markers for HBV DNA level detection in pregnant women. HBeAg is a marker of viral replication, thus HBeAg detection can help to identify high-risk pregnant women in a resource-limited setting. In addition, a meta-analysis has shown that HBeAg detection was accurate in classifying women with high HBV DNA titers (> 5.3 Log_{10} IU/mL), with a sensitivity of 99.5% (95%CI: 91.7-100) and specificity of 62.2% (95%CI: 55.2-68.7), respectively [54].

Additionally, the use of quantitative HBsAg detection in areas of limited resources is also encouraged. A 2016 study showed a positive correlation between maternal serum quantitative HBsAg level and HBV DNA VL, which can accurately predict maternal HBV DNA level, particularly in those with high VL levels (6–8 Log_{10} IU/mL)[55]. A more recent study showed that maternal serum quantitative HBsAg level was also strongly correlated with HBeAg status, with higher quantitative HBsAg levels in the HBeAg seropositive group compared to the HBeAg seronegative group (3.88 *vs* 2.86 Log_{10} IU/mL). Serum quantitative HBsAg level can also be used to predict HBV infection in the placenta (with 90% sensitivity and 83% specificity) and umbilical cord blood (with 82% sensitivity and 96% specificity). Therefore, maternal serum HBsAg level can be used as a surrogate test for HBeAg and HBV DNA VL tests in pregnant women with HBV infection[25].

Prenatal intervention

HBIG is a purified solution of human immunoglobulin containing high titers of anti-HBs. HBIG is widely administered to rapidly neutralize HBV by activating the complement system and strengthening humoral immunity. Prenatal injection of HBIG in pregnant women could theoretically prevent intrauterine infection by transferring maternal antibodies to the fetus. HBIG injection in CHB mothers (either HBsAg seropositive or HBeAg seropositive) will offer protection to infants by passive diffusion of the antibody through the placenta[56-62]. The effect of this passive diffusion of the antibody was found to be greatest during the last trimester of pregnancy[63].

A meta-analysis in 2017 showed that HBIG administration was effective in preventing hepatitis B occurrence in newborn infants born to mothers who were HBsAg- and HBV DNA-positive[63]. However, another study found that HBIG administration alone did not prevent MTCT, especially in mothers with high HBV DNA VL[64]. As there is an additional potential risk of immune complex disease due to the specific binding of HBIG to HBsAg, the European Association of the Study of The Liver (EASL) still does not indicate the use of HBIG in HBsAg-positive mothers[65].

Instead of administering HBIG in the third trimester of pregnancy, antiretroviral therapy (ART) may be a better choice in preventing MTCT. The use of ART has been widely accepted and applied in clinical practice and has a good result in blocking HBV vertical transmission from mother to infant. It has been reported that antiviral therapy in mothers with high HBV DNA VL (≥ 7 Log_{10} IU/mL) significantly reduced the rate of MTCT from 14.3% to 0%[66]. Several types of nucleos(t)ide analogue (NA) drugs including lamivudine (3TC), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF) have been used in CHB pregnant women to study the safety and efficacy of these antiviral prophylaxes in mothers and infants to reduce HBV MTCT rate[60-62].

Antiviral prophylaxis for CHB pregnant women has now been recommended by the three major liver study associations, the Asia Pacific Association for the Study of the Liver (APASL), EASL, and the American Association for the Study of the Liver (AASLD). The APASL has recommended that pregnant females with HBV DNA levels ≥ 5.3 Log_{10} IU/mL should receive antiviral prophylaxis to prevent MTCT. TDF is the recommended antiviral prophylaxis, which should be initiated at 24-28 weeks of the gestation period, in addition to appropriate immunoprophylaxis for the infants[7]. Similarly, the EASL also advised TDF treatment as antiviral prophylaxis for pregnant women with HBV DNA levels of ≥ 5.3 Log_{10} IU/mL or HBeAg-positive at week 24-28 of the gestation period, which should be continued for up to 12 weeks after delivery[65]. The AASLD specifically recommend the use of TDF to prevent the risk of MTCT in HBsAg-positive pregnant women with high HBV DNA levels (≥ 5.3 Log_{10} IU/mL) and to minimize the risk of viral resistance emergence during treatment. However, the AASLD discourages the use of ART to reduce the risk of perinatal HBV transmission in HBsAg-positive pregnant women with low HBV DNA levels (< 5.3 Log_{10} IU/mL)[33].

In line with this, the WHO has just released their new guidelines for CHB infection prevention, diagnosis, care, and treatment, and updated their recommendation for antiviral prophylaxis in pregnant women. To prevent MTCT of HBV, TDF treatment is recommended for high HBV VL (≥ 5.3 Log_{10} IU/mL) or HBeAg-positive, HBsAg-positive pregnant women, starting from the second trimester of pregnancy until delivery or until completion of vaccination in the infants.

Where testing of HBV DNA and/or HBeAg is lacking, TDF treatment for all HBV-infected (HBsAg-positive) pregnant women is recommended[59].

A 2019 meta-analysis compared the effectiveness of 3TC, LdT, and TDF in reducing MTCT rate. It was shown that only LdT treatment was associated with a reduced rate of HBsAg positivity in infants; and higher rates of HBeAg loss, reduced HBV DNA levels, and normalization of alanine aminotransferase (ALT) levels in mothers. None of the NA drug treatments were associated with any preterm births, congenital malformations or low birthweight. Furthermore, LdT treatment also significantly lowered both the MTCT rate and infants' HBV DNA positivity at birth, and increased HBV DNA level suppression in mothers[67]. A 2020 real-world study also compared the efficacy and safety of 3TC and LdT treatment in more than 2000 pregnant mothers with high HBV DNA levels (> 6 Log_{10} IU/mL) in China to prevent MTCT. They found that antiviral treatment, either with 3TC or LdT, which was initiated in the third trimester, greatly reduced the MTCT rate compared to untreated mothers. There were also no differences in perinatal complications in the mothers or growth parameters in the infants[68]. These results indicate the recommended use of LdT treatment for CHB pregnant mothers to prevent MTCT. However, there are concerns regarding the low genetic barrier of LdT, which may allow for the emergence of viral resistance-associated mutations[7]. As such, NA drug treatment history in pregnant women is crucial to determine which type of drugs can be administered. In treatment-naïve pregnant mothers, 3TC or LdT treatment is preferred, as antiviral resistance to 3TC or LdT is rare due to the brief length of drug exposure. However, in previously treated subjects, TDF treatment is advisable due to its favorable resistance profile. Furthermore, TDF has demonstrated a good long-term fetal safety profile[65].

Recently, more studies have compared the efficacy and safety of TDF treatment in pregnant women. A 2020 observational study in 644 pregnant women who were HBeAg-positive and had a high HBV DNA VL (≥ 5.3 Log_{10} IU/mL), showed that treatment with LdT and TDF significantly lowered maternal HBV DNA level at the time of delivery, with an average decrease of two Log_{10} IU/mL, and thus consequently reduced the MTCT rate. No adverse events were observed, thus both NA drugs are safe for mothers and newborns. In addition, pregnant women treated with TDF in the second trimester showed an even more significant reduction in HBV DNA level compared to those treated in the third trimester. This study showed that TDF has better efficacy than LdT in reducing maternal HBV DNA levels[69]. With regard to HBV genetic diversity, a 2022 Chinese study demonstrated that HBV genotype may be associated with response to antiviral treatment in pregnant women, as measured by changes in the HBV DNA level. HBV genotype has been identified as an independent factor related to the change in HBV DNA level, but not HBV RNA level, after antiviral treatment (either with LdT or TDF)[70].

Despite the good safety profile of TDF, its use has been correlated with kidney and bone loss problems. Therefore, another form of tenofovir, tenofovir alafenamide fumarate (TAF) is also currently used to manage HBV infection. However, there are still limited data on the effect of TAF treatment in pregnant women with CHB. A prospective observational study studied the effect of TAF treatment during pregnancy in 232 CHB women with high HBV DNA VL (≥ 5.3 Log_{10} IU/mL) in preventing MTCT. In comparison with TDF, TAF treatment was well tolerated with similar safety profiles in mothers and infants. Overall, both TAF and TDF treatment in the study cohort resulted in a reduced rate of MTCT to 0%[71]. These results indicate that TAF can also be safely used for antiviral prophylaxis in CHB pregnant women.

Additionally, a systematic review in 2023 found that no significant difference in the safety and efficacy of TDF and TAF treatment in highly viremic CHB pregnant women. Both NA drug treatments resulted in significant reductions in maternal HBV DNA levels during delivery and the MTCT rate reduced to 0%[72]. Another recent meta-analysis also concluded that TAF treatment showed good efficacy as antiviral prophylaxis in reducing MTCT rates with good safety profiles in both mothers and infants[73].

Infant immunoprophylaxis

Infants are more vulnerable to HBV infection. Infants who contract HBV infection during their first year of life are more likely to develop CHB. Several prevention strategies, such as active and passive immunoprophylaxis, can protect infants from HBV infection. Active immunoprophylaxis is given through HBV vaccination, while passive immunoprophylaxis is obtained through HBIG injection shortly after birth. Overall, the percentage of children under five years old with CHB has now decreased, from 5% in the pre-vaccination era (1980s–2000s) to around 1% in 2019[74]. These numbers represent a noteworthy progress in the global effort to reduce HBV infection in children.

Some studies have shown that infant immunization can effectively prevent MTCT. Regardless of the mother's HBV status, the WHO guideline advises that all newborns should receive HepB-BD within 24 hours after birth, followed by additional doses at one and six months of age. HBIG is also recommended for infants of HBsAg-positive mothers[46,47]. However, implementation of the guidelines may differ regionally, based on the HBV prevalence in that region. In China, which has a high prevalence of HBV infection, the implementation of three doses of the HepB vaccine for infants born to HBsAg-positive mothers is reported to result in a significant decrease in MTCT risk of up to 95%[75]. In addition, in low-prevalence HBV regions in Europe including Germany, Ireland, the Netherlands, and the United Kingdom, HepB-BD is typically administered to infants between the ages of six to nine weeks[76].

The effectiveness of the HepB-BD vaccine can be seen in the Americas and European countries. In the Americas, 57% of the countries have a national plan in place for viral hepatitis prevention, treatment, and control. They have also implemented infant vaccination programs for over 20 years. The region is considered successful in eliminating MTCT of HBV, as evidenced by the very low prevalence (< 0.1%) of hepatitis B in children under five years old. In addition, the three-dose vaccination coverage rate for children aged below one year was 87%, with birth dose vaccination coverage rate of 76% in 2017[77].

European countries also made significant progress toward hepatitis B control between 2016 and 2019. In Europe, the number of countries that have achieved the coverage targets for Hep-BD, all three doses of the HepB, and HBV screening in pregnant women are 35, 19, and 17, respectively. Italy and the Netherlands are the first two countries in Europe who

have been validated by the WHO as being successful in their hepatitis B control program, with HBsAg prevalence of 0.5% among the vaccinated cohort[77,78].

The efficacy of HBIG injection in preventing HBV infection in infants remains controversial. HBIG administration was shown to reduced MTCT in infants of HBsAg seropositive women compared to no intervention (6% *vs* 21%, risk ratio = 0.30, 95%CI: 0.20-0.52)[46,47,63]. However, several studies in infants born to HBsAg-positive/HBeAg-negative mothers have shown that the addition of HBIG injection to HBV vaccination dose did not provide an additional protective effect compared to HBV vaccination alone[79,80]. Another study has also corroborated these findings, and found that in infants born to HBeAg seronegative mothers, HBV vaccination alone is sufficient and effective in reducing the rate of MTCT without the addition of HBIG injection[58]. As HBeAg is not routinely tested in HBsAg seropositive pregnant women, HBIG injection would still be beneficial for infants born to these women, especially in high HBV prevalence areas, to reduce cases of infantile fulminant hepatitis[81]. In Taiwan, the government still encourages HBIG injection in infants of HBsAg seropositive mothers, regardless of the maternal HBeAg status, as the cost of HBIG is considered cheaper than HBeAg testing[81].

The protective effect of HBIG injection may also relate to the time of administration. A few studies had demonstrated that earlier immunoprophylaxis administration may provide greater protection against MTCT. A 2021 study in China where both HBIG and HepB-BD were injected in newborns within an hour after delivery, the overall MTCT rate was 0.9% [82]. Similarly, a recent study also confirmed the vital role of the administration time of combined immunoprophylaxis (both HBIG and HepB-BD) for infants born to CHB mothers. Infants that were administered combined immunoprophylaxis within two hours of birth had an MTCT rate of 0.32% (1/308) compared to 2.73% (8/293) in those who received combined immunoprophylaxis between two and 12 hours after birth[83].

A concern regarding the use of HBIG immunoprophylaxis in infants is the rate of OBI. OBI cases, defined as HBsAg seronegative but HBV DNA seropositive, were more commonly found in neonates who received both the HepB vaccination and HBIG doses, possibly due to the added immune pressure induced by the HBIG injection[79,80]. A study in China looking at the status of HBV infection in neonatal HepB- and HBIG-vaccinated infants born to HBsAg seropositive mothers found that 3.9% (3/77) of the infants were HBsAg-positive and 36.4% (28/77) were identified as OBIs. Furthermore, infants with OBI had lower levels of anti-HBs but higher levels of antibody against hepatitis B core antigen (anti-HBc). However, this high anti-HBc level was found to diminish after the 18-month follow-up period followed by HBV DNA seronegativity. This study concluded that the detected OBI in these vaccinated infants was not likely an established OBI, but a transient persistence of HBV DNA accompanied by passive transference of anti-HBc from the CHB mothers[84].

Passive transference of HBV antibodies from mothers to infants was also observed in a 2020 prospective cohort study in China. The authors found that despite the zero MTCT rate (shown as HBsAg seronegativity in infants) and anti-HBs seropositivity in the infants (with high antibody titers), a small proportion of the infants still expressed anti-HBc and anti-HBe (antibody to HBeAg) during the 7-month follow-up period after birth[85]. Thus, these findings indicated that even though perinatal transmission did not occur, HBV antibodies may still be able to enter the infants due to passive transfer from the mothers through intrauterine transmission[85].

PVST

The effectiveness of MTCT prevention can be determined by PVST. This test should be conducted after the last dose of the infants' HBV vaccine to determine the outcome of the given immunoprophylaxis.

The WHO recommend that PVST should be performed for all HBV-exposed HepB vaccinated infants around 1 to 2 months after the completion of the HepB vaccination series, when the antibody response is usually greatest. The infants will be tested for: (1) HBsAg, to determine chronic HBV infection; and (2) Anti-HBs, to detect immunity against HBV, where an anti-HBs titer of ≥ 10 mIU/mL indicates protective immunity[5]. The PVST is needed to monitor the outcomes and impact of MTCT intervention strategies, by determining the proportion of infants who are (1) Infected with HBV; (2) Uninfected and have protective immunity against HBV, and (3) Uninfected but not responding to HepB vaccination[6,7].

A 2017 retrospective study in China identified that, in 438 pairs of mothers and infants, 5.3% infants who had received complete HepB doses were HBsAg seropositive, with a PVST time around 1 to 8 months after the last HepB dose[86]. Similarly, in 2017 another PVST study in China reported that HBsAg positivity rate was 3.7% with an anti-HBs positivity rate of 90.9% in 1025 maternal-infant pairs. They also identified that maternal HBeAg status was correlated with the infant's positivity for both HBsAg and anti-HBs. Additionally, the highest anti-HBs levels in the infants were detected by PVST assessed at 1 to 2 months following the final HepB dose, and prolonged PVST intervals resulted in decreased anti-HBs geometric mean concentration[75].

The timing of PVST may influence the proportion of non-responders. Huang *et al*[87] showed that when PVST was assessed at an interval of 1, 2, 3, 4, 5, 6, and 7 to 8 months after the last HepB dose, the non-response rate was 1.6%, 1.1%, 0.9%, 0.7%, 1.1%, 0.7%, and 5.7%, respectively, with a significantly higher non-response rate in PVST at 7 to 8 months. In addition, anti-HBs titers also declined significantly in infants with medium anti-HBs responses when PVST is performed at a longer interval from the final HepB dose. These results indicate that the optimal PVST interval for infants born to HBsAg-positive mothers is at seven months of age or around one month after HepB vaccination series completion[87].

A more recent prospective observational PVST study in China confirmed the previous findings. Among 2120 mother and infant pairs, the HBsAg positive rate was 0.77%, anti-HBs positive was 96.84%, and both the HBsAg and anti-HBs seronegative rate was 2.39%. Among 34 infants with double seronegative results, 15 had received all three doses of HepB [88]. A recent study analyzing PVST results among at-risk babies born to HBV positive mothers from 2008 to 2022 in China showed that the MTCT rate between infants born to HBsAg-positive/HBeAg-negative and HBeAg-positive mothers was significantly different (0.75% *vs* 6.33%). In addition, the MTCT rate for infants born to HBeAg-positive mothers receiving antiviral prophylaxis was 1.72%[89].

The PVST is important for determining MTCT rate in at-risk infants born to HBV-infected mothers; however, there is also a risk of low compliance in PVST. In a retrospective cohort study in Fujian, China, only 4988 infants out of 8474 at-risk infants were eligible for PVST. Twenty-percent of infants (n = 994) were lost to follow-up in the testing cascade, with 55% of parents refusing venous blood sample collection or failure of field sample collection, 16% transferred out of the region, and 10% of parents chose to perform independent PVST without reporting the results. It was also identified that the high PVST noncompliance rates was associated with infants born to HBeAg positive mothers (OR = 1.2, 95%CI: 1.1-1.4)[90].

Vaccine non-responders may influence the effectiveness of HepB vaccination in HBV-exposed infants. For at-risk infants who were still negative for HBsAg and anti-HBs after receiving the complete HepB vaccine series, the WHO recommended that they received a revaccination followed by a repeat PVST 1 to 2 months after the last vaccination dose [6,7]. A 2012 study in China demonstrated the effect of the vaccine after revaccination in non-responding infants. From 1814 infants, 3.1% were identified as non-responders (anti-HBs titers < 10 mIU/mL) and 28.4% were low-responders (anti-HBs titers ≥ 10 and < 100 mIU/mL). After HepB revaccination, 14.7% became low-responders and 85.3% became responders in the 34 non-responding infants. On the other hand, in the 74 low-responding infants, 78.4% shifted to responders while 21.6% remained low-responders[91].

A recent retrospective study has shown that, for non-responders, an additional fourth vaccine booster dose may be beneficial to improve the anti-HBs response. It was found that a fourth dose of the vaccine resulted in detectable anti-HBs levels in 52.2% (105/201) of HepB vaccine non-responders[92]. Additionally, another study has shown that those with pre-booster anti-HBs levels of 2 to 9.9 mIU/mL had a higher possibility of responding to an additional vaccine booster dose compared to those with anti-HBs levels < 2 mIU/mL[93].

Another issue associated with HBV vaccination is vaccine escape mutations (VEMs). The appearance of VEMs has not been intensively studied; however, detecting the emergence, rate, and clinical significance of these variants is important for HBV management, especially in high HBV prevalence regions. There is a lack of viral genetic data on VEMs in the population, although current genomic data indicates a low prevalence of individual VEMs[47,94]. A phylogenetic analysis showed that VEMs may arise independently of antiviral treatment or HBV vaccine exposure, but these variants can be found across different HBV genotypes, with the highest prevalence identified in genotype C[94]. As such, the emergence of VEMs remains a potential challenge in association with infant HBV vaccination programs[46,47].

COMBINATION OF ANTIVIRAL AND IMMUNE PROPHYLAXIS TO REDUCE MTCT

Research shows that the combination of passive and active immunization in infants born to HBsAg-positive mothers reduced the rate of MTCT. However, this immunization approach cannot fully eradicate the risk of MTCT, as immunoprophylaxis failure has been reported in vaccinated infants[95]. Delayed vaccination and inadequate initial injections in infants, along with high maternal HBV DNA levels, have been associated with these immunoprophylaxis failures[96]. In addition, epidemiological and modeling studies have also shown that HBV immunization alone would not be sufficient to reduce the WHO's target of 0.1% HBsAg prevalence goal in children by the year 2030[7,45]. Therefore, additional approaches are needed to achieve a zero MTCT rate. Many studies in the last decade have shown the promising use of antiviral prophylaxis in CHB pregnant women, in combination with immunoprophylaxis for infants, to reduce the risk of MTCT, as antiviral treatment in pregnant women showed a good safety and efficacy profile in lowering HBV DNA level [95]. The mechanisms of both prophylaxes are described in Table 1.

A 2020 study compared the MTCT rate in neonatal HBV-vaccinated infants born to antiviral-treated and non-treated CHB pregnant women. Antiviral treatment (either with LdT, TDF, or 3TC) resulted in zero MTCT rate (n = 60) compared to 0.1% (3/30) in infants born to non-treated mothers and 39.2% (11/28) in the control group[97]. Accumulating evidence from randomized controlled trials (RCTs) has also shown the effectiveness of combined intervention to prevent HBV MTCT[46,47]. Data from 15 RCTs with 2706 infants from HBsAg seropositive mothers showed that reduced MTCT risk is higher in HBIG- and HepB-vaccinated infants born to highly viremic mothers (HBV DNA ≥ 5.3 Log_{10} IU/mL) who received antenatal NA prophylaxis [relative risk (RR) = 0.47, 95%CI: 0.29-0.75], compared to: (1) Vaccinated infants born to highly viremic but untreated mothers (RR = 0.31, 95%CI: 0.10-0.99); (2) Infants receiving combined HBIG and HepB vaccination (RR = 0.37, 95%CI: 0.210-0.67), and (3) Infants receiving only HepB vaccination (RR = 0.32, 95%CI: 0.21-0.50) [98].

A meta-analysis in 2022 analyzed 300 studies worldwide to determine the rate of HBV MTCT under different prophylaxis regimens. The overall MTCT incidence rate without prophylaxis was 31.3%, which varied in different regions. Infant vaccination reduced the MTCT risk in HBeAg seropositive mothers from 82.9% to 15.9% and from 10.3% to 2.3% in HBeAg seronegative mothers. A further reduction in MTCT rate to 0.3% (95%CI: 0.1%-0.5%) was achieved by combining maternal peripartum NA prophylaxis and infant vaccination. In addition, the risk of HBV transmission can be stratified based on the maternal HBV DNA VL, where MTCT incidence increased when the maternal HBV DNA level was higher than 4.29 Log_{10} IU/mL[46,47,99].

CHALLENGES AND EFFORTS

There are several challenges that may occur in implementing an antiviral and immune prophylaxis approach for MTCT prevention in HBsAg seropositive pregnant women. These include the costs and availability of antiviral and immune prophylaxis, ideal time to initiate antiviral prophylaxis, lack of access to HBV DNA tests, cases of immunoprophylaxis

Table 1 The mechanism of hepatitis B immune and antiviral prophylaxis to reduce mother-to-child transmission

MTCT Intervention	Mechanism	Ref.
Immunoprophylaxis		
Hepatitis B immunoglobulin	Blocks viral attachment and subsequent entry of HBV into hepatocytes; neutralizes circulating HBV and target infected cells *via* antibody-mediated immune response; has to be administered within 24 hours of birth	[56, 57]
Hepatitis B vaccine	Induces active immunity by producing antibodies that target the surface antigen of HBV; given in three doses, at 0, 1, and 6 months, with the first dose recommended within 24 hours after birth	[58]
Antiviral prophylaxis		
Lamivudine, Telbivudine	Deoxycytidine nucleoside analogues; acts as obligate DNA chain terminators; have low genetic barrier to resistance that can lead to drug resistance; not recommended as first-line antiviral therapy for pregnant women	[59, 60]
Entecavir	Deoxyguanosine nucleoside analogue; inhibits replication of HBV by inhibiting HBV polymerase; halts HBV DNA elongation after incorporating a few additional bases; has high genetic barrier to drug resistance	[61]
Tenofovir disoproxil fumarate, Tenofovir alafenamide fumarate	Nucleos(t)ide analogues; inhibits viral replication by inhibiting HBV polymerase; have a high genetic barrier to drug resistance; tenofovir disoproxil fumarate is the current recommended antiviral therapy for pregnant women to prevent MTCT	[62]

MTCT: Mother-to-child transmission; HBV: Hepatitis B virus.

failure in infants, in addition to the lack of trained health-care workers, lack of capacity, and limitations of infrastructure in some HBV endemic countries[7,45].

The cost and access to antiviral prophylaxis

The cost and access to antiviral prophylaxis could pose a serious issue for HBV MTCT prevention programs in pregnant women. TDF is now listed on the WHO list of essential medicines and is considered of low cost; however, access to TDF in some HBV prevalent regions remains poor[46,47]. In China, the lowered cost of TDF to less than USD 1.50 *per* month and ensuring its availability in most hospitals in the country, greatly supported the success of their SHIELD HBV MTCT prevention program[46]. In African countries, access to TDF for HBV patients may be possible through the existing human immunodeficiency virus (HIV) program, since TDF is also used for HIV treatment with already well-established supply chains[100]. In addition, it is estimated that 6.1% of women with HIV infection were also coinfected with HBV[7, 45], thus TDF treatment in pregnant women in Africa will be beneficial for the prevention of both HIV and HBV transmission in the region.

In the case of low accessibility to TDF in pregnant women, the use of combined antivirals (for example TDF with other anti-HBV agents) or more reliance on an immunoprophylaxis program may be considered for MTCT prevention[46,47, 101]. A 2018 clinical trial performed in 331 pregnant women in Thailand showed that the administration of neonatal HBIG and full doses of HBV vaccination in infants born to HBeAg seropositive women were sufficient to reduce the MTCT rate. Furthermore, it was found that additional TDF treatment did not result in a significantly lower rate of HBV transmission[101]. A 2023 retrospective study in Thailand performed cost-effectiveness analyses of the following different TDF-based intervention strategies: (1) TDF to eligible mothers and HBIG for all infants; (2) TDF to eligible mothers and HBIG for infants from HBeAg-positive mothers, and (3) TDF to eligible mothers without HBIG for infants. Their analyses showed that the HBIG-free strategy was the most cost-saving intervention, with 0 to 1.4% transmission rates, making it an ideal strategy for high HBsAg seropositive prevalence but resource-constrained populations[102].

The ideal time to initiate antiviral prophylaxis

Another issue related to antiviral prophylaxis in pregnant women is when to start treatment. The recommended initiation time for antiviral prophylaxis is after 24 weeks gestation. However, it is unclear whether antiviral treatment in CHB pregnant women can be initiated before 24 weeks gestation. A study has shown that the reduction in HBV DNA level was more significant in pregnant women who started treatment in the second trimester (< 27 weeks) compared to the third trimester (> 28 weeks)[69]. A significant reduction in HBV DNA level was also observed in pregnant women treated with TDF in the second trimester compared to those treated in the third trimester[69]. A network meta-analysis comparing the efficacy and safety of antiviral therapy in pregnant women also concluded that treatment administered during the early or middle pregnancy period had better efficacy in HBeAg seropositive pregnant women with a high HBV DNA VL (≥ 6 Log_{10} IU/mL). Furthermore, this particular effect was consistent, regardless of the NA drugs used[103].

A 2020 prospective cohort study in China enrolled 136 CHB women to assess the safety and efficacy of antiviral treatment before and during pregnancy. A small proportion of the women with active CHB was treated with either TDF or LdT prior to pregnancy to normalize their liver enzymes, and continued with TDF or LdT administration throughout the entire pregnancy. The study showed that these women showed no differences in obstetric-related complications compared to the other three groups of pregnant women who received antiviral therapy as follows: (1) In early pregnancy (< 24 weeks); (2) In late pregnancy (> 24 weeks), or (3) In late pregnancy, but with high HBV DNA VL (> 6 Log_{10} IU/mL). In addition, all their infants (who had received neonatal HBIG dose and a complete series of HepB vaccination) showed

negative HBsAg status after the 7-month follow-up period, with no differences in the infants' rates of congenital malformation and other growth indicators[85].

Current evidence on the use of antiviral prophylaxis in HBsAg seropositive mothers is positive, as there were no observed adverse events for the mothers or infants[69,85]. To date, no NA drugs have been associated with obstetric-related complications in mothers or congenital malformations in infants[67,69,85], thus all NA drugs are considered safe for mothers and newborns. However, there are still limited long-term safety data on the effect of antiviral prophylaxis use during pregnancy[103], and whether antiviral prophylaxis is safe to use in multiple pregnancies. Thus, more data are needed to fully understand the effect of this treatment on mothers and infants.

The costs of immunoprophylaxis

Despite the satisfactory effect of infant immunoprophylaxis, vaccine delivery including maintenance of the cold chain logistics, consistency and equity of supply, and timely administration may hinder MTCT elimination[46,47]. One strategy to improve feasible implementation of HBIG and HepB for infants of HBV-positive mothers within one hour of birth is to ensure the vaccine supply both in the delivery room and postnatal ward[82,104]. Current monovalent HBV vaccine is considered low cost; however, the total health care cost also includes the cost for the infrastructure and personnel. Therefore, the total cost for the patient might actually be higher than the cost of the vaccine dose itself[46,47]. Regardless, the rate of infants receiving the appropriate HepB dose at birth has increased in areas where local health care policies mandate for HBV vaccination shortly after birth with a constant supply of available vaccine in the labor and maternity wards[105,106].

Taiwan serves as a success story for infants' HBV vaccination program. As the first nation to implement an HBV vaccination program for infants in 1984, they gradually expanded their vaccination target to increase vaccination coverage, from only infants with high-risk mothers to all infants regardless of maternal HBsAg status. Now, they are targeting all infants who missed their vaccination as newborns and adolescents. After 30 years of implementation, Taiwan has successfully decreased the prevalence of HBsAg from 9.8% to 0.5% in individuals ≤ 30 years old and to ≤ 1% among 5-year-old children. Consequently, they also managed to reduce the incidence of fulminant hepatitis in infants and HCC in the population[81]. Similarly, the success of the HBV vaccination program in China is attributed to the government's commitment to reduce the MTCT rate. Early in the program, parents had to cover the cost of the infants' HBV vaccination, which affected the rate of vaccine coverage in the country. However, in 2002, the Chinese government successfully built a collaborative project with the Global Alliance for Vaccines and Immunization (GAVI) to ensure all children receive HBV vaccination, even in the poorer western provinces. This collaboration has increased the vaccination coverage rate in infants from 30% in 1992 to 93.4% in 2005, with a reduction of HBsAg prevalence from 2.1% to 1%[107]. Indeed, GAVI has provided support on vaccine-related financial and logistical costs since 2001, including vaccine cost reduction to below USD 1 *per* dose and the availability of pentavalent vaccines (DPT-HepB-Hib), has greatly increased the vaccine coverage rate in GAVI-supported countries[108].

Availability of HBIG supply is a costly investment, and as such HBIG is often not readily available in low-income countries. To try to overcome this shortcoming, a clinical trial was performed in Cambodia to assess the feasibility of the immunoglobulin-free strategy for MTCT in a limited-resource region. More than 1000 HBsAg-positive pregnant women were recruited in the TA-PROHM study from 2017 to 2020, and 28% (338/1194) of these women received TDF treatment. In infants not receiving HBIG injection, the MTCT rate was zero (n = 227) in those born to women who received TDF for more than four weeks before delivery. However, in those born to women who received TDF for less than four weeks, the MTCT rate was 8% (3/36). These results show that even without neonatal HBIG administration, TDF treatment was sufficient to reduce the MTCT rate[109]. In addition, determination of the mothers' eligibility for TDF treatment can be performed using the HBeAg rapid detection test and an ALT-based algorithm[109,110], which would be more feasible in a limited-resource setting with high HBV prevalence.

Cases of immunoprophylaxis failure in infants

Despite the protective effect of immunoprophylaxis administration in infants of HBsAg-positive mothers, cases of immunoprophylaxis failure have been reported. A 2021 Chinese study reported nine cases of immunoprophylaxis failure (n = 982) in newborns receiving both HBIG and HepB-BD within an hour after delivery, who were born to women with a high HBV DNA VL (> 6.4 Log_{10} IU/mL)[82]. In infants born to HBeAg-positive mothers, the frequency of immunoprophylaxis failure was higher at 5.2% (16/306) compared to those born to HBeAg-negative mothers. This immunoprophylaxis failure was associated with very high HBV DNA levels (≥ 8 Log_{10} IU/mL, OR = 4.53, 95%CI: 1.19-17.34), inadequate initial injections (OR = 7.69, 95%CI: 1.71-34.59), and delayed vaccination time (OR = 4.14, 95%CI: 1.00-17.18)[96].

A 2021 birth cohort study in central Vietnam discovered that in children born to HBsAg seropositive mothers, 13.1% (16/122) who received a complete series of HepB vaccination had HBV infection at the 2-year follow-up period, and 20.5% (9/44) who received incomplete HepB doses were also infected. In addition, in children born to HBeAg-positive mothers, 28.3% (15/53) who received a complete series of HepB vaccination had HBV infection, while 53.3% (8/15) who received incomplete HepB doses also became infected[111]. This study showed the importance of post-vaccination serological testing for vaccinated infants born to HBsAg seropositive mothers, to determine the seroprotective level of anti-HBs in these children. In addition, other vaccination strategies may be needed to reduce the rates of immunoprophylaxis failure in high HBV prevalent regions, by changing the dose of the HepB vaccine and/or HBIG for at-risk infants.

A multicenter study in China enrolled 955 pairs of infants and their HBsAg-positive mothers. The infants all received HBIG injection (at 0 and 1 month) and either 10 μg or 20 μg HepB (at 0, 1, and 6 months). The results showed that the immunoprophylaxis failure rate in the 20 μg HepB group was not significantly different compared to the 10 μg group, regardless of the maternal HBV DNA level, with both doses having good safety profiles in the infants. However, the

higher HepB dose was associated with a significant reduction in the low-response rate (anti-HBs titer ≥ 10–100 IU/L) and middle-response rate (anti-HBs titer 100–1000 IU/L), and increased the high-response rate (anti-HBs titer ≥ 1000 IU/L) in infants born to mothers with low HBV DNA levels (< 5 Log_{10} IU/mL)[112].

With regard to HBIG doses, there are currently two recommended HBIG doses used in several countries for newborn injection, 100 IU and 200 IU. Wei *et al*[113] has shown that for infants born to HBsAg-positive mothers, the infection rate in infants injected with either 100 or 200 IU HBIG did not significantly differ, with respective prevalences of 1.5% (8/545) and 1.9% (12/632). The respective anti-HBs positive rates in the two groups were 98.5% (529/537) and 98.2% (609/620), with comparable anti-HBs levels of 707.95 mIU/mL and 602.56 mIU/mL at the 7-month follow-up period. However, in the 200 IU HBIG group, one non-responding infant became HBsAg seropositive at the 12-month follow-up period[113]. A RCT of 331 pairs of infants and HBsAg- and HBeAg-positive mothers in China confirmed the previous finding. It was found that in vaccinated infants born to HBsAg- and HBeAg-positive mothers, the higher dosage of HBIG (200 IU) did not provide an additional protective effect against MTCT compared to the lower HBIG dose (100 IU). However, in relation to the cost of infant vaccination, the analysis demonstrated that the use of three-doses of HepB vaccine and a single dose of 100 IU HBIG was the more cost-effective approach in preventing HBV MTCT in the country[114].

Availability of HBV DNA testing

To successfully implement a prenatal intervention in HBsAg seropositive pregnant women, access to laboratory testing for HBV screening is crucial. Poor access to laboratory-based screening of HBV seromarkers (HBsAg and/or HBeAg) and HBV DNA VL quantification are often reported in resource-limited countries. Furthermore, in areas where the appropriate laboratory facilities are already available, the high cost of the tests might also be an issue[46,47].

HBV DNA VL quantification is considered the best method to determine whether a CHB pregnant woman is eligible for TDF treatment, as most of the antiviral prophylaxis guidelines use the maternal HBV DNA level of ≥ 5.3 Log_{10} IU/mL as the cut-off for antiviral treatment initiation. However, not all countries have the resources and facilities to perform routine HBV DNA quantification tests. As such a reliable surrogate marker for HBV DNA level is needed, especially in a limited-resource setting. HBeAg detection and a quantitative HBsAg level test have been identified as possible alternative cost-effective tests for HBV DNA level quantification[7,45].

A 2020 Cambodian study in 515 HBsAg-positive women demonstrated the potential use of a combined algorithm of the HBeAg rapid diagnostic test and ALT levels for identifying women eligible for TDF treatment. It was found that a positive HBeAg rapid test and ALT threshold level of 40 IU/L had a sensitivity and specificity of 79% and 93% for HBV DNA level > 5.3 Log_{10} IU/mL, and 88% and 93% for HBV DNA level > 7.3 Log_{10} IU/mL, respectively[110]. HBsAg levels have also been shown to positively correlate with HBV DNA levels in HBeAg seropositive pregnant women, with a correlation of low HBsAg levels of < 3 Log_{10} IU/mL with HBV DNA levels < 6 Log_{10} IU/mL. Thus, HBsAg quantitative level may serve as a good VL predictor in HBeAg-positive pregnant women[115]. Additionally, the detection of hepatitis B core-related antigen (HBcrAg) has also shown good correlation with HBV DNA level, where a value of 5.3 Log U/mL is equal to a HBV DNA level of ≥ 5.3 Log_{10} IU/mL. Thus, HBcrAg may also be used as an alternate serological marker to identify high viremia in treatment-naïve CHB patients[65,116].

The development of a rapid, affordable, and point of care test (POCT) or near-POCT for HBV DNA may also reduce the dependency on HBeAg testing[46,47]. Furthermore, the availability of an inexpensive POCT for HBV DNA may simplify the need for two separate tests for HBsAg and HBV DNA VL into a single HBV test for diagnostic and risk stratification purposes in pregnant women[46,47]. A widely available HBV DNA test would also allow for the identification of OBI in at-risk cases, although OBI is not considered a significant risk factor for MTCT as OBI cases typically have low HBV DNA levels[46,47]. In China, a multilevel step HBV MTCT prevention program was introduced to solve the issue of lack of trained healthcare workers and limitations of infrastructure. The multilevel approaches in their SHIELD program allows for proper training of healthcare workers and gradual improvement in healthcare infrastructure to ensure a good compliance rate (83.2%) in antiviral-treated pregnant women[46].

Another available approach to improve accessibility to HBV testing is by combining resources with the HIV infection elimination program. Established infrastructure for HIV MTCT prevention can be shared for the HBV MTCT prevention program due to their similar approaches, especially in resource-poor settings in Africa[117]. The use of dried blood spots for hepatitis B testing may also be considered, especially in low-resource settings with limited access to well-equipped health care facilities[100].

Lack of awareness of HBV screening

There are several identified barriers that may impede a successful HBV prevention MTCT program, which include lack of awareness of HBV screening and the benefit of HBV vaccination for at-risk infants and their caregivers. The WHO has identified that HBV immunoprophylaxis program expansion is greatly impacted by the local and diverse characteristics of the target population and the cultural beliefs and political acceptance in the country[46,47,108]. As such, enhancing health education and awareness of the risk factors associated with HBV infection, chronic liver disease progression, and effective screening and treatment regimens are crucial, along with advocacy and adequate representation for specific at-risk populations including rural communities, migrant populations, and marginalized groups[46,47].

In Africa, where some countries still have no dedicated HBV programs, expanding the existing HIV MTCT prevention program will enable HBV screening tests for pregnant women, resulting in improved identification and access to care for HBV mono infected pregnant women[100]. Meanwhile, in high-income countries, HBV undiagnosed individuals usually come from vulnerable populations, including intravenous drug users, homeless persons, and illegal immigrants[108]. These people are often difficult to reach, therefore community-based HBV screening and outreach program may be beneficial in identifying these at-risk individuals[46,47].

Increasing awareness of HBV screening in pregnant women may also be beneficial for MTCT prevention programs. In Nigeria, mothers with good knowledge of HBV (receiving tertiary education as an indicator) were more likely to vaccinate their newborns[105]. Similarly, in China, mothers with high education levels were the most likely to perform PVST follow-up after their infants' vaccination[88]. Overall, it is crucial to combine effective treatment and comprehensive policies in infection prevention, political commitment, financial structure, stakeholder engagement, and healthcare system integration[108].

CONCLUSION

Vast and significant efforts to reduce the risk and prevalence of HBV MTCT have been noted in many countries, including in HBV endemic regions in the Asia Pacific region. However, additional approaches are needed to achieve a zero MTCT rate, including HBV screening of pregnant women, interventions in HBV transmission during delivery, and infant immunoprophylaxis. These should also be accompanied by the availability and the affordability of HBV tests, HBIG, and antiviral therapies.

FOOTNOTES

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