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Review paper

Hepatitis B virus infections in pregnant women and children in the era of HBV elimination

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Abstract

In the hepatitis B virus (HBV) elimination strategy announced by the World Health Organization (WHO) in 2016, one of the main aspects is the prevention of vertical infections. In the prevention of vertical HBV infections, chemoprophylaxis with tenofovir is recommended from the 28th week of pregnancy in women with a high viral load (HBV DNA > 2×10^5 IU/ml) or the presence of HBeAg in the serum and active-passive immunoprophylaxis (HepB-BD+ HBIG) in all newborns born to mothers infected with HBV. Attention was paid to the incidence of latent HBV infections among children and adolescents and the role of the vaccine dose and additional hepatitis B booster vaccination in the prevention of HBV, especially in highly endemic areas and risk groups. The role of the age of initiation of therapy in the context of functional cure was indicated.

Key words: HBV, vertical infections, prevention, occult HBV infections, children.

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Introduction

Hepatitis B virus (HBV) infection in a pregnant woman can be associated with adverse outcomes such as gestational diabetes, intrahepatic gestational cholestasis and preterm labor. It always poses a risk of vertical transmission. In the HBV elimination strategy announced by the World Health Organization (WHO) in 2016, prevention of vertical transmission (mother-to-child transmission – MTCT) is one of the main aspects. It is known from the natural history of HBV infection that vertical infections and infections in the first year of life have the highest rate of chronicity, so it can be assumed that they account for a large part of the global burden of chronic hepatitis B.

Prevention of vertical HBV infections

Mother-to-child transmission remains one of the most common routes of HBV infection. According to estimates, there are approximately 6.4 million children under the age of five chronically infected with HBV worldwide. High levels of HBV DNA, the presence of HBeAg in the pregnant woman's serum, placental barrier failure and fetal immune immaturity are the risk factors for chronic HBV infection. Active-passive immunization (anti-HBV vaccine and hepatitis B immunoglobulin [HBIG]) on the first day of life of the newborn and antiviral therapy from the 28th week of pregnancy in women with high viral load (HBV DNA > 2×10^5/ml) are the most important methods of MTCT HBV prophylaxis [1].

For the prevention of vertical HBV infections, WHO recommends widespread vaccination of infants with at least three doses of anti-hepatitis B vaccine with special attention to timely administration of the birth dose (HepB-BD) as soon as possible after birth, preferably within 24 hours, and in countries with high endemicity up to 2 hours after birth. Since 1992, the WHO has recommended that HepB vaccination be included in the Expanded Program on Immunization (EPI). High birth-dose immunization rates at the right time and completion of a series of anti-HBV vaccinations are the most important interventions to

reduce MTCT of HBV as well as HBV transmission in early childhood and achieve HBV elimination goals. Completion of the vaccination series leads to immune protection in more than 95% of children. Since 2020 the WHO has recommended that HBV-infected pregnant women with a high viral load (HBV DNA ≥ 200,000 IU/ml) should receive antiviral prophylaxis with tenofovir administered from 28 weeks of pregnancy at least until delivery. If access to HBV DNA determination is difficult, HBeAg determination is acceptable. This recommendation provides access to chemoprophylaxis for vertical HBV infection for women in low- and middle-income countries (LMICs) and complements the three-dose anti-HBV vaccination in all infants. Another recommendation is the use of HBV immunoglobulin (HBIG) in the newborn of an HBV-infected mother to further reduce the risk of MTCT of HBV. The indicators of the effectiveness of prophylaxis of vertical HBV infection are the following: achieving an HBsAg prevalence of less than 0.1% among children under 5 years and a MTCT rate of less than ≤ 2% [2, 3] (Fig. 1).

Nayagam *et al*. conducted a study to evaluate the cost-effectiveness of perinatal antiviral prophylaxis (PAP) in women at high risk of HBV vertical transmission (HBV DNA ≥ 200,000 IU/ml or presence of HBeAg) and a theoretical simplified strategy whereby PAP is administered to all HBV-infected pregnant women (HBsAg present) without risk stratification. Three strategies were evaluated: PAP in women with high HBV DNA levels (PAP-VL), PAP in pregnant women with current HBeAg (PAP-HBeAg) and PAP for all pregnant women with current HBsAg (PAP-universal), compared to MTCT prophylaxis with neonatal hepatitis B vaccination. It has been estimated that the addition of PAP-VL to HepB-BD could prevent about 1.1 million new neonatal infections by 2030 and about 3.2-3.4 million new neonatal infections by 2100. In theory, the strategy of offering PAP to all HBV-infected women could be a cost-effective alternative, depending on the prevailing costs of antiviral diagnosis and therapy [4].

Liu *et al*. analyzed the association between serum HBcrAg levels and chronic hepatitis B (CHB) exacerbations among 172 pregnant women with CHB in the immune tolerance phase who received short-term antiviral therapy with tenofovir (TDF), discontinued at 12 weeks postpartum. Exacerbations of CHB occurred

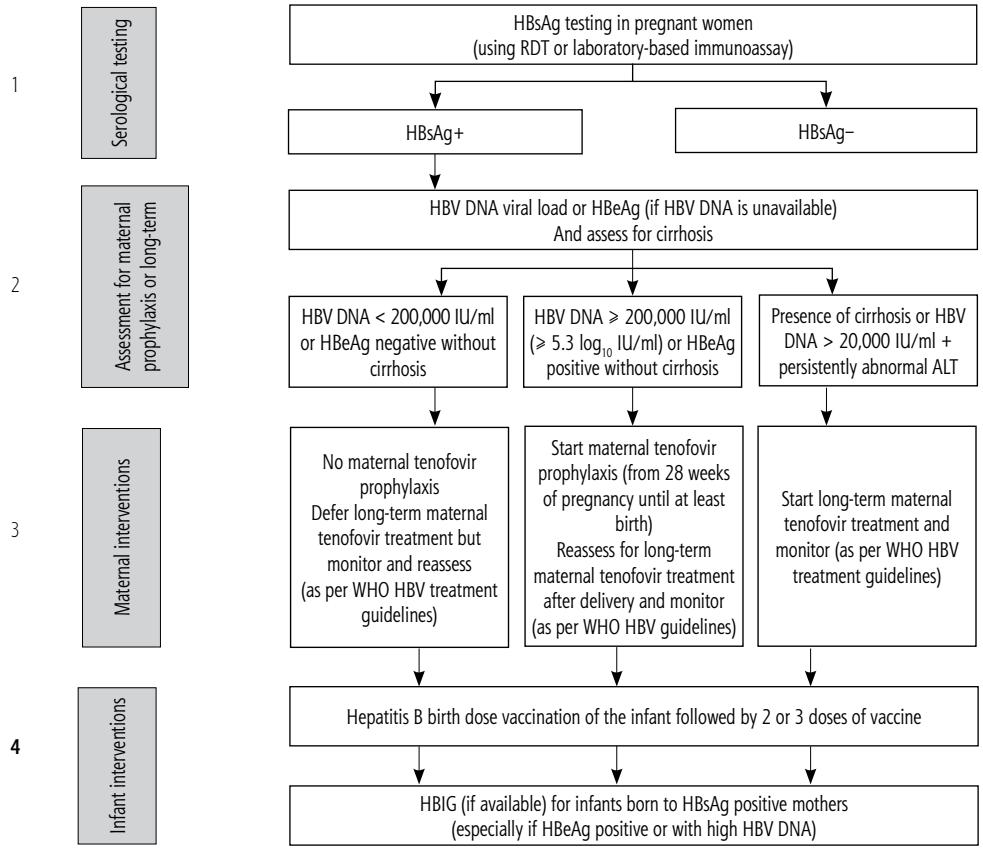

Fig. 1. Algorithm on maternal and infant interventions for prevention of mother-to-child transmission [3]

in 52/172 (30.2%) of the patients. Serum HBcrAg concentrations at week 12 postpartum were shown to be an independent risk factor for CHB exacerbations. For this reason, women with serum HBcrAg levels ≥ 0.275 are recommended to continue antiviral therapy with TDF [5].

There has been an ongoing discussion for many years about the impact of the mode of delivery on the risk of HBV MTCT. A meta-analysis of 19 articles describing 11,144 HBV-infected pregnant women, of whom 5251 delivered by natural childbirth and 5893 had cesarean sections, showed that cesarean section reduces the risk of MTCT (OR = 0.62, 95% CI: 0.48-0.81, $p < 0.001$) and should be used for MTCT prevention [6].

Pan *et al*. analyzed whether cesarean section and lack of breastfeeding could prevent MTCT in HBV-infected women with current HBeAg who did not receive antiviral treatment during pregnancy. The study enrolled 852 mothers and 857 newborns. All newborns of those mothers received active-passive immunoprophylaxis for HBV infection. The risk of HBV infection in the group of newborns born by cesarean section was lower than in the group of vaginal births (RR = 0.58, 95% CI: 0.46-0.74). The risk of MTCT in the group of artificially fed babies was significantly lower (RR = 0.74, 95% CI: 0.56-0.98). Cesarean section and no breastfeeding reduce the risk of MTCT in newborns of HBV-infected mothers with HBeAg present who did not receive antiviral treatment during pregnancy [7].

Occult HBV infection in children

Occult hepatitis B infection (OBI) is a specific form of HBV infection that can lead to hepatocellular carcinoma in adults. Latent HBV infections are common and clinically relevant, but insufficiently studied and understood. They are a particular problem in HBV endemic areas and in high-risk groups worldwide. HBV DNA testing remains an expensive and inaccessible method in many highly HBV endemic countries with limited economic resources. The rationale for population-based serologic studies of latent HBV infection and prospective studies of the mechanisms and consequences of latent HBV infection, considering latent HBV infection as a variable that could potentially jeopardize HBV elimination, is supported [8].

Based on 50 studies, Wu *et al*. estimated the overall prevalence of OBI in children and adolescents at 7.5%. It varied according to the population studied: in the HIV-infected population it was 24.2%, in the healthy population it was 0.8%, in the general population it was 3.8%, in children born to HBsAg-positive mothers it was 6.4%. Depending on the serological profile of HBV infection, the incidence of OBI in HBsAg-negative, anti-HBc-positive patients was 6.6%, in HBsAg-negative, anti-HBc-negative patients 3.0%, in HBsAg-negative, anti-HBs-negative patients 4.6%. Despite anti-HBV vaccination and the use of HBIG, OBI is common in high-risk children and adolescents [9].

Recently, there have been reports of OBI in newborns of HBV-infected mothers despite immunoprophylaxis at birth, raising concerns that the current dose of anti-HBV vaccine may not be completely effective. Several studies have shown that the 20 μg dose of the anti-HBV vaccine has good immunogenicity and safety in newborns. Among 549 infants born to HBsAg and HBeAg-positive mothers with HBV DNA ≥ 6 $\log_{10}$ IU/ml, 349 infants were vaccinated with the 10 μg/dose HepB vaccine in combination with HBIG, and 200 infants with the 20 μg/dose HepB vaccine in combination with HBIG. Anti-HBs levels in the group of infants vaccinated with the 10 μg dose were significantly lower than in the group vaccinated with the 20 μg dose at both 7 months of age (652.48 vs. 1541.72 mIU/ml, $p < 0.001$) and at 12 months of age (257.44 vs. 1073.41 mIU/ml, $p < 0.001$). The incidence of OBI in the group of infants vaccinated with the 10 μg dose was significantly higher than in the group vaccinated with the 20 μg dose at both 7 months (21.55% [25/116] vs. 7.56% [9/119], $p = 0.002$) and 12 months of age (17.07% [14/82] vs. 6.90% [6/87], $p = 0.041$). Analysis of OBI according to anti-HBs concentration showed that the incidence of OBI in infants with anti-HBs concentration < 100 mIU/ml was higher than in infants with anti-HBs antibodies ≥ 100 mIU/ml (35.71% [5/14] vs. 13.12% [29/221], $p = 0.036$). The study showed that increasing the vaccine dose from 10 μg to 20 μg significantly increased anti-HBs antibody levels and reduced the incidence of OBI in infants born to HBV-infected mothers with high HBV DNA levels. A dose of 20 μg HepB is suggested for this high-risk population [10].

Li *et al*. studied the effect of a HepB booster dose on OBI in 236 HBsAg-negative children of HBV-infected mothers. 100/236 children received a booster dose of HepB between the ages of 1 and 3 years. The incidence of OBI varied during follow-up and was 37.14% (78/210), 19.09% (42/220), 20.85% (44/211), 31.61% (61/193), 8.65% (18/208) and 12.71% (30/236) at 7 months, 1, 2, 3, 4 and 8 years of age, respectively. The incidence of OBI in children of HBsAg-positive mothers was high, and a booster dose of HepB in infancy reduced the incidence of OBI in children of HBsAg-positive mothers. Children with OBI not only pose a risk of reactivation of HBV infection, but also may be a potential source of HBV transmission and pose a chal-

lenge in controlling HBV infection and achieving the goal of HBV elimination by 2030. Of particular note is the detection of HBV DNA in serum and the incidence of OBI in children of HBV-infected mothers, following immunoprophylaxis. Only about 30% of the children studied never developed OBI, suggesting that children born to HBV-infected mothers should be monitored for serum HBV DNA evaluation [11].

Treatment of HBV infection in children

There have been few published reports on the use of antiviral therapies in children with chronic hepatitis B with a high viral load and normal or slightly elevated ALT activity. Recently, much attention has been given to functional cure, which is defined as loss of HBV DNA, loss or seroconversion of HBeAg and loss of HBsAg, with or without seroconversion [12].

Li *et al*. presented an analysis of the efficacy of antiviral treatment in 48 children with CHB, with a high HBV viral load and normal or slightly elevated serum ALT activity. Thirty-two children received interferon α (IFN-α) monotherapy, IFN-α therapy with the addition of a nucleoside analog (NA), or combination therapy of IFN-α and NA; 16 children in the control group received no antiviral treatment. After 36 months, the cumulative functional recovery rate was 56.25% (18/32) in the treatment group and 0% (0/16) in the control group ($p < 0.001$). There was a rapid reduction in viral titer in the treatment group compared to baseline and almost complete viral suppression six months after antiviral treatment in cured children. After 36 months, the rate of serum HBV DNA loss was 100% in cured children and 64.29% (9/14) in untreated children ($p < 0.001$). HBeAg seroconversion rates were significantly higher among cured children than among untreated children ($p < 0.001$). Functional cure was associated with younger age (1-6 vs. 7-14 years, $p = 0.013$), CD8+ T lymphocyte count and B lymphocyte count. No serious adverse events were observed. Antiviral treatment enabled functional cure of CHB in a high percentage of children with high viral load and normal or slightly elevated alanine transaminase (ALT) activity. Younger age and high peripheral lymphocyte counts were associated with functional cure [13].

Wu *et al*. studied the effect of the age of treatment initiation on the outcomes in 306 previously untreated children with CHB. The study participants were divided into three groups according to the age at which they started antiviral treatment: 1-3 years, 4-6 years and 7-17 years. The endpoints of this study were HBsAg loss, HBeAg clearance and HBV DNA undetectability. The authors showed that HBsAg loss and HBeAg clearance were frequently observed in children with CHB treated with antiviral therapy, and that the age of initiation of the treatment may be an indicator of response to treatment, including HBsAg loss and HBeAg clearance [14].

In Poland, two HBV infections were reported in 2021 in infants born to HBV-infected women. The immunization status of children at age 2 with three doses of anti-HBV vaccine decreased slightly compared to 2020 at 89.3%. Restrictions related to the COVID-19 pandemic in Poland have had less of an impact on HBV screening in pregnant women and on the performance of hepatitis B vaccination in newborns and infants. In 2021, there were no acute cases among children and young adults up to age 28. In 2021 the highest rate of new hepatitis B diagnoses, at 9.48/100,000, was in the 30-34 age group. In this age group, the rate was higher among women than among men, at 9.85/100,000. Among women aged 25-34, the high detection rate, which exceeds the rate among men, remains due to the screening of pregnant women. Among the youngest children up to the age of 4, 2 infections were registered in newborns born to HBV-infected women, and one infection detected in a 2-year-old child, probably acquired in connection with medical procedures during multiple hospital stays (the child was vaccinated with the full series). Among children aged 5-14 years, no chronic infection was detected; in the group aged 15-19 years, 1 infection was detected in an unvaccinated person. Infection acquired from an HBV-infected mother was diagnosed in two cases (in children born in 2020 and 2021). In 2021, the vaccination status of children from the year 2020 vaccinated with three doses of hepatitis B vaccine was 89.3% overall for Poland (in 2020 the status for children from 2019 was 89.7%). The rate of vaccination with at least two doses of hepatitis B vaccine for children in 2020 in 2021 was 97.2% overall. An unfavorable downward trend in the vaccination status of children in their second year of life with three doses of hepatitis B vaccine has been identified. A further decrease in the vaccination status of the youngest children leads to an increase in the risk of HBV infection in the mandatory vaccination population and to the loss of one of the previously achieved goals of the strategy for the elimination of HBV, i.e. vaccinating 90% of children in the second year of life with 3 doses [15].

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