Antenatal Anti-viral Therapy and Postvaccination Serologic Test for Hepatitis B Infection: Are we Following Guidelines?

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Abstract
Several official recommendations were published in the management of hepatitis B surface antigen (HBsAg)-positive pregnant women to prevent mother-to-infant transmission of hepatitis B virus (HBV) by antenatal anti-viral therapy. Infants born to women with HBV infection should have serological review following completion of a vaccination schedule at age 9 - 18 months to determine infant outcomes after prophylaxis. Postvaccination serologic testing is critical for guiding medical management of infants born to HBsAg-positive women and identifying infants with HBV infection. However, study results in the literature demonstrated that although adherence to the vaccination schedule was mostly satisfactory, increased commitment is still required from health providers to ensure that infants born to infected mothers are fully vaccinated and tested at the appropriate age. Following the guidelines and monitoring the intervention are essential, not only for the health of the infant but also to make sure the HBV elimination program is achieving the expected results.

Keywords: Antenatal Anti-viral Therapy; Postvaccination Serologic Test; Hepatitis B Infection

Introduction
Hepatitis B virus (HBV) infection is a major global health problem. According to World Health Organization estimates, 257 million people are chronically infected with hepatitis B [1]. Hepatitis B virus infection not only causes acute or chronic hepatitis, but also leads to severe long-term, life-threatening complications. In Asia, HBV infection acquired by mother-to-infant transmission (MTIT) is considered one of the major causes of chronic infection. Approximately 90% of infected infants develop chronic HBV infection, with a 15% - 25% risk for premature death from cirrhosis, liver failure or hepatocellular carcinoma [2,3].

Mother-to-infant transmission
The mechanisms of vertical HBV transmission include intrauterine infection and peripartum transmission [4]. Maternal HBV viral load is considered another important viral risk factor for MTIT. Many studies have shown increased risk of MTIT was related with higher maternal levels of HBV-DNA. Zhang, et al. reported maternal-positive HBV-DNA was associated with higher MTIT incidence compared with negative [5]. In our previous study in Taiwan, Wen, et al. found that predictive MTIT incidence at maternal viral load levels of 6, 7, 8 and 9 log10 IU/mL were 2.5%, 5.7%, 12.4%, and 24.7%, respectively [6].

Standard HBV immunoprophylaxis course
To prevent perinatal HBV transmission, the Advisory Committee on Immunization Practices (ACIP) of Centers for Disease Control and Prevention (CDC) recommends that infants born to HBsAg-positive women receive postexposure prophylaxis with hepatitis B vaccine and...
hepatitis B immune globulin (HBIG) within 12 hours of birth and complete the 3-dose hepatitis B vaccine series [7]. Currently, universal infant HBV vaccination has been implemented in 180 countries worldwide [8]. In Taiwan, the first country to launch a nationwide universal hepatitis B vaccination program [9], the HBV infection rate decreased from 38 to 4.6% in children after implementation of universal hepatitis B immunization [10].

**Antenatal anti-viral therapy**

A recent study from the CDC demonstrated that more than 90% caregivers follow the standard prophylaxis recommendation [11]. However, they also found there is still a subset of pregnant women fails to protect against MTIT under standard guideline. These women almost have high levels of HBV DNA and are hepatitis e antigen positive. Several studies have been initiated to determine if using antiviral treatment in these women to reduce their HBV DNA would be effective besides the standard prophylaxis protocol and they have promising results [12,13]. The studies using tenofovir (Category B drug) beginning at 28 - 32 weeks of gestation and continuing until 1 - 2 months postpartum have demonstrated decreased transmission rates compared to control [14-16]. This practice is now enrolled as part of the American Association for the Study of Liver Diseases (AASLD) HBV guidelines for management of pregnant women [17].

The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level > 200,000 IU/mL (1 million copies/mL). Antiviral therapy is started at 28 - 32 weeks of gestation and discontinued at birth to 3 months postpartum. Women should be monitored for ALT flares every 3 months for 6 months [17]. According to the Society for Maternal-Fetal Medicine’s recommendation, in pregnant women with HBV infection and viral load > 6 - 8 log 10 copies/mL, HBV-targeted maternal antiviral therapy should be considered for the purpose of decreasing the risk of intrauterine fetal infection. In pregnant women with HBV infection who are candidates for maternal antiviral therapy, they suggest tenofovir as a first-line agent [18]. The European Association for the Study of the Liver also recommends in all pregnant women with high HBV DNA levels (> 200,000 IU/ml) or HBsAg levels > 4 log10 IU/ml, antiviral prophylaxis with TDF should start at week 24 - 28 of gestation and continue for up to 12 weeks after delivery [19].

**Postvaccination serologic testing**

The combination of immunoprophylaxis in newborns and antiviral prophylaxis for mothers with a high viral load is found feasible to completely interrupt MTIT of HBV [20]. However, infants born to HBV-infected mothers, especially those with high viral load, are still at risk of infection despite standard prophylaxis. These high-risk infants should be screened to identify those with HBV infection [4].

To determine infant outcomes after postexposure prophylaxis, ACIP recommends that infants born to women with HBV infection should have serological review following completion of a vaccination schedule at age 9-18 months. Postvaccination serologic testing (PVST) is critical for guiding medical management of infants born to HBsAg-positive women, identifying infants with HBV infection and in need of further care, and monitoring progress toward the elimination of MTIT of HBV. In concordance with prenatal screening strategy, some countries screen infants born to both HBsAg- and HBeAg-positive mothers [4,7], but some only screen infants born to HBsAg-positive mothers due to financial considerations.

**Are we following guidelines?**

To evaluate the implementation of these recommendations, CDC assessed outcomes at age 24 months among infants born to HBsAg-positive women enrolled in Enhanced Perinatal Hepatitis B Case Management Projects (EPHPB) [7]. Of 4,214 EPHBP-managed infants who completed ≥3 hepatitis B vaccine doses, 63.7% had reported PVST results, 13.3% had reported PVST results but infant age was unknown, and 23.0% had no reported PVST results. Of 2,683 infants with PVST results by age 24 months, 93.3% were protected, 1.2% were infected, 3.2% remained susceptible, and 2.3% had indeterminate results.
In a retrospective review of all HBsAg-positive women and their infants in a large teaching NHS Trust in Leicester, UK [21], 7% of pregnancies occurred in women who were taking antenatal antivirals. 176 infants were born to 140 HBsAg-positive women through 172 pregnancies. Two (1.1%) were vertically infected. Only 81.1% infants completed all HBV vaccinations and 79.5% completed serology testing. 96.4% women were referred to the hepatitis clinic, but 30% disengaged from clinic follow-up.

In a PVST of infants born to hepatitis B surface antigen positive mothers in 4 provinces of China, 65.6% of infants born to HBsAg positive mothers were enrolled in PVST after receiving 3 doses of hepatitis B vaccines, 3.7% infants were tested HBsAg positive, 90.9% infants were anti-HBs positive when tested at 7 - 24 months of age [22]. In another study from Australia, of the 66 infants for whom data were available, 98.5% had appropriately received four doses of hepatitis B vaccine in infancy. Only 19/66 (29%) infants had documented follow-up serology results [23].

The above study results demonstrated that although adherence to the vaccination schedule was mostly satisfactory, increased commitment is still required from health providers to ensure that infants born to infected mothers are fully vaccinated and tested at the appropriate age.

**Conclusion**

In pregnant women with HBV infection and high viral load, HBV-targeted maternal antiviral therapy should be considered for the purpose of decreasing the risk of intrauterine fetal infection. A birth dose of HBIG and hepatitis B vaccination of those infants born to mothers with HBV infection has significantly reduced the chance of MTIT. An important reminder for caregivers seeing infants that have received a complete course of HBV immunoprophylaxis is to assess the infants at 9-18 months for presence of HBsAg antibody and absence of HBsAg. Following the guidelines and monitoring the intervention are essential, not only for the health of the infant but also to make sure the HBV elimination program is achieving the expected results.

**Conflict of Interest**

The author declares no conflicts of interest that pertain to this work.

**Bibliography**


