

Brief Communication: Perinatal Transmission of Hepatitis B and Prevention Strategy

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Introduction

Hepatitis B is a disease of global significance. The World Health Organization (WHO) estimates that this virus currently infects 350 million people worldwide, and over three quarters of those affected are of Asian ethnicity.¹ Hepatitis B is an important cause of progressive liver failure or liver cancer, complications that kill approximately 1 million people globally. In endemic regions such as Asia and Africa, HBV infection is often acquired early in life, either vertically from perinatal transmission or horizontally from contact with other infected individuals.² In Asia, perinatal transmissions account for at least 25% of chronic hepatitis B; moreover, the transmission rates can increase to about 90% for mothers with high serum HBV DNA titers.² Since HBeAg positive chronic hepatitis B is associated with higher levels of HBV replication, the perinatal transmission rates were as high as 80-90% among HBeAg-positive women compared to 10-20% among HBeAg-negative women.³ Universal screening of all pregnant women during their pregnancy is essential to identify the ones with the highest risk of transmitting HBV to their infants.

Immunization in Preventing Vertical Transmission

Having established the importance of perinatal transmission and the need to screen pregnant women, the next logical question is how best to interrupt transmission between the mother and her newborn child. Currently, the Center for Disease Control recommends a combination of passive

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(hepatitis B immune globulin [HBIG] at birth) and active (hepatitis B vaccination) immunization for infants born to HBsAg-positive mothers.

Recommendations for preventing maternal-neonatal transmission of HBV:⁴

- Administer HBIG within 12 hours of birth (200 IU intramuscularly).
- Administer full course of HBV vaccine at a contralateral site (first dose within 48 hours of birth, usually concurrent with HBIG).
- HBIG may interfere with ability of live vaccines to induce immunity; live vaccines should be delayed for 3 months.

Generally, this immunization strategy is 85-95% effective in preventing neonatal infection. However, the risk of vertical transmission can still occur in the setting of significant viremia. A meta-analysis showed that among 705 Dutch infants born to women with HBeAg-positive chronic hepatitis B, 1.1% became HBsAg carriers by one year of age despite receiving immunoprophylaxis.⁵ Maternal serum HBV DNA level was the only factor significantly associated with infant infection. A recent study from Australia reported results on 138 pregnancy outcomes. It reported similar conclusion that HBV perinatal transmission was restricted to HBeAg-positive mothers with HBV DNA levels higher than 10⁸ copies/ml.⁶ Intrauterine/ transplacental transmission of hepatitis B during the antepartum phase can also occur especially among HBeAg positive mothers with high level of viremia and in the setting of threatened preterm labor or partial placental leakage.^{7,8} Intrauterine/transplacental transmission is believed to be a significant cause of passive-active immunoprophylaxis failure.⁸

Safety of Hepatitis B Therapy During Pregnancy to Prevent Mother-To-Child Transmission

Data are limited regarding the safety of HBV therapy during pregnancy (**Table 1**). Lamivudine, adefovir, and entecavir have been labeled as pregnancy category C drugs by the US FDA, indicating that they exert teratogenic or embryocidal effects in animals and have not been evaluated in controlled studies in humans. Tenofovir and telbivudine are category B drugs, meaning that they carry no teratogenic or embryogenic

risks in animal studies, or they have shown a risk in animal studies that was not reproduced in human studies. Interestingly, lamivudine was classified by US FDA as a category B drug for HIV indication. Interferon and peginterferon are contraindicated during pregnancy due to their antiproliferative effects.⁹ However, no outcomes following accidental exposure to peginterferon have been reported.¹⁰

Several studies have shown that the use of lamivudine towards the end of pregnancy may reduce the likelihood of mother-to-child transmission. van Zonneveld and colleagues administered lamivudine 150 mg daily to 8 HBsAg-positive women during the last month of pregnancy.¹¹ Infants in the study received appropriate immunoprophylaxis with HBIG and HBV vaccination. The rate of perinatal transmission decreased from 7 in 25 in the control group (28%) to 1 in 8 in the lamivudine arm (12.5%); no side effects were observed in mothers or infants.

Xu and colleagues conducted a multicenter, randomized, double-blind, placebo-controlled study comparing lamivudine vs placebo during the last 8 weeks of pregnancy in 120 women with serum HBV DNA >1000 MEq/mL; infants in both groups received HBIG and HBV vaccination soon after birth. A significantly lower proportion of infants in the lamivudine group vs the placebo group tested positive for HBsAg at Week 52 (18% vs 39%; $P = .014$).¹² The rates of adverse events were similar in the two arms.

Despite the potential benefit of lamivudine for reducing vertical transmission, antiviral therapy during pregnancy remains controversial. Namely, the studies evaluating lamivudine in pregnancy were not adequately powered or controlled to prove efficacy definitively.⁹ Tenofovir use during pregnancy and breastfeeding needs further evaluation given the potential adverse effect of osteopenia.⁹ Similar, the use of Telbivudine is controversial due to its potential cause of myopathy.

Lamivudine remains the treatment of choice to use during the third trimester of pregnancy to prevent HBV transmission, as it has been studied more extensively in pregnancy than any other agent.¹³ The 2007 report of the Antiretroviral Pregnancy Registry states that among 1888 women exposed to lamivudine during the first trimester of pregnancy, the birth defect rate was 2.9%. Among 3463 women exposed during the second or third trimester, the rate was 2.6%.¹³ These rates are similar to the reported 3% birth defect rate in the general population.¹⁴ Data on Tenofovir use during the first trimester of pregnancy from the Antiretroviral Pregnancy Registry is also encouraging with a birth defect rate of 2.2% among live births. It is a potential medication to consider during pregnancy if the issues on bone density are satisfactorily resolved.

Safety of Breastfeeding

In the 1980s and 1990s, several groups advised against breastfeeding in women with chronic hepatitis B based on reports that HBV could be transmitted through breast milk. However, recent evidence suggests that when appropriate immunoprophylaxis is used, breastfeeding does not increase the risk of transmitting HBV to the infant. Hill and colleagues compared transmission rates among 101 breastfed infants and 268 formula-fed infants, all of whom received HBIG at birth and the full course of HBV vaccinations.¹⁶ Overall, 0 of the 101 breastfed infants and 9 of the formula-fed infants (3%) were HBsAg-positive after the initial HBV vaccinations ($P = 0.063$). However, the potential role of HBeAg positivity in increasing the risk of vertical transmission through breastfeeding deserves further evaluation.

Summary

- Perinatal transmission is a significant source of HBV infection, particularly among HBeAg-positive women with high levels of viremia.
- Administration of HBIG and HBV vaccine within 12 hours after birth can prevent perinatal transmission in majority of cases.
- Women with high HBV DNA levels can potentially transmit HBV to their infants, even with HBV vaccine and HBIG administration.
- Although there is no consensus regarding the use of anti-HBV therapy during pregnancy, treatment during third trimester on women with high levels of viremia may reduce the risk of perinatal transmission.
- Breastfeeding does not appear to increase the risk of vertical transmission when infants receive appropriate immunoprophylaxis, but further research is necessary to confirm.

References

1. Maynard JE. Hepatitis B: global importance and need for control. *Vaccine*. 1980;8(suppl):18-20.
2. Margolis HS, Alter JH, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. *Sem Liver Dis*. 1991;11(2):84-92.
3. Gambarin-Gelwan M. Hepatitis B in pregnancy. *Clin Liver Dis*. 2007;11(5):945-996.
4. Zuckerman JN. Review: hepatitis B immune globulin for prevention of hepatitis B infection. *J Med Virol*. 2007;79(7):919-921.
5. del Canho R, Grosheide PM, Mazel JA, et al. Ten-year neonatal hepatitis B vaccination program, the Netherlands, 1982-1992: protective efficacy and long-term immunogenicity. *Vaccine*. 1997;15(15):1624-1630.
6. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *MJA*. 2009;190(9):489-492.
7. Zhang SL, Yue YF, Bai GQ, Shi L, Jiang H. Mechanism of intrauterine infection of hepatitis B virus. *World J Gastroenterol*. 2004;10(3):437-438.
8. Xu DZ, Yan YP, Choi BC, et al. Risk factor and mechanism of transplacental transmission of hepatitis B virus: a case-control study. *J Med Virol*. 2002;67(1):20-26.
9. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology*. 2007;45(4):1056-1075.
10. Ross B. Safety of antiviral therapy of chronic hepatitis B during pregnancy. NIH Hepatitis B Workshop; April 6-8, 2006; Bethesda, MD.

11. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. *J Viral Hepat.* 2003;10(4):294-297.
12. Xu WM, Cui YT, Wang L, et al. Efficacy and safety of lamivudine in late pregnancy for the prevention of mother-child transmission of hepatitis B: a multicentre, randomised, double-blind, placebo-controlled study. *J Viral Hepat.* 2009;16(2):94-103.
13. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2007. Wilmington, NC: Registry Coordinating Center; 2007 (available from: www.APREgistry.com).
14. Centers for Disease Control and Prevention (CDC). Improved national prevalence estimates for 18 selected major birth defects- United States, 1999-2001. *MMWR Morb Mortal Wkly Rep.* 2006;54(51):1301-1305.
15. Terrault NA, Jacobson IM. Treating chronic hepatitis B infection in patients who are pregnant or are undergoing immunosuppressive chemotherapy. *Semin Liver Dis.* 2007;27(suppl 1):18-24.
16. Hill JB, Sheffield JS, Kim MJ, Alexander JM, Sercely B, Wendel GD. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. *Obstet Gynecol.* 2002;99(6):1049-1052.

Table 1. Use of Anti-HBV Agents in Pregnancy.

Agent	Pregnancy Class	Animal Studies	Human Experience
Lamivudine	C (HBV) B (HIV)	Not teratogenic in rats, rabbits to 35x the human dose; embryotoxic at human doses in rabbits but not rats	> 4000 women
Adefovir	C	No toxicity in rats or rabbits to 23x the human dose; embryotoxic and teratogenic at 38x the human dose	No adequate, well-controlled studies in pregnant women
Entecavir	C	No toxicity in rats or rabbits to 212x the human dose; embryotoxic and teratogenic at 883-3100x the human dose in rats and rabbits	No adequate, well-controlled studies in pregnant women
Tenofovir	B	No toxicity in rats or rabbits to 14-19x the human dose	No adequate, well-controlled studies in pregnant women
Telbivudine	B	No toxicity at 6x or 37x the human dose in rats or rabbits, respectively	No adequate, well-controlled studies in pregnant women

(Table modified from Terrault and Jacobson¹⁵)

