Commentary

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What is the Reason for Poor Outcome of Antepartum Immunoprophylaxis of Hepatitis B Immunoglobulin in Prevention of Vertical Hepatitis B Transmission?

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Hepatitis B virus (HBV) infection is a serious global health problem, with 2 billion people infected worldwide, and 350 million suffering from chronic HBV infection. Hepatitis B infection is the 10th leading cause of death worldwide, and results in 500,000 to 1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HCC accounts for 320000 deaths per year [1]. The risk of perinatal HBV transmission is greater for infants born from women who are positive for both HBsAg and HBeAg. The risk ranges from 70 to 90% for infants born from mothers who are positive for both HBsAg and HBeAg, in contrast to the 10-40% risk in infants born from mothers who are positive for HBsAg but negative for HBeAg [2, 3]. Comparatively, East Asia has been found to have a higher prevalence of HBeAg positive mothers and a greater risk of perinatal transmission from HBeAg positive mothers than sub-Saharan Africa [4].

More than 20 years have elapsed since 1984, when vaccination against hepatitis B began, first with a plasma-derived vaccine and later a recombinant DNA-derived vaccine, and during this period important changes have taken place in several aspects of this disease; the acute and chronic infection rates, the mortality of fulminant hepatitis B in infants; and the incidence of HCC have been effectively reduced by approximately 25%. Vaccination during childhood has produced adequate protection for up to 20 years later [5]. Safe and effective vaccines against HBV infection have been available since 1982. The implementations of mass immunization programs, which have been recommended by the World Health Organization since 1991, have dramatically decreased the incidence of HBV infection among infants, children, and adolescents in many countries [1]. Vaccination alone did not induce immunity against hepatitis B in high-risk children (whose mothers are HBsAg positive) and it seems that routine screening of pregnant women is necessary for determining whether neonates need hepatitis B immunoglobulin (HBIG) after birth [6]. On the other hand, with combination of HBV vaccine and HBIG in neonatal the chance of transmission can be avoided significantly, but not totally [7].

We read with great interest the valuable article by Xiao *et al.* [8]. The aim of this study was to explore the possible efficacy of using HBIG during the third trimester of pregnancy to prevent intrauterine transmission of HBV. A total of 469 pregnant women with chronic HBV infection, that consisted of 126 women with HBeAg positive (group 1) and 343 women with HBeAg negative (group 2) were evaluated. Ninety-five women in group 1 and 222 women in group 2 were treated with HBIG during the third trimester of pregnancy. All infants in each

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group were received 100 IU of HBIG intramuscularly within 12h of birth plus the first of a 3-dose vaccination schedule. Among infants born from HBeAg positive mothers, 15.8% were positive for HBsAg at birth and 7.4% at the six months, if their mothers had treated with HBIG during pregnancy, and these rates were significantly lower than the corresponding rates of 38.7% and 22.6% for those whose mothers had not received HBIG treatment (P<0.05). Among infants born from HBeAg negative mothers, however, no significant differences were found whether the mothers had been treated or not.

We believe there are some important points, which had been missed by authors. First of all, the most important factor affecting intrauterine and peripartum transmission is the maternal HBV-DNA level at the time of delivery and near it [9-11]. Some studies have shown that, especially when HBV-DNA is $\geq 10^8$ copies/mL, it has a significant correlation with neonatal HBV infection [10, 12]. Therefore, these groups should be compared regarding serum HBV-DNA levels. It is expected that HBIG regimen is successful, when the HBV-DNA levels reduce significantly at the time of delivery. One study showed administration of HBIG during pregnancy had reduced the maternal HBV-DNA levels of 56 cases from $\log_{10}$ 7.38±1.17 copies/mL to $\log_{10}$ 5.28±2.77 copies/mL (P<0.05) [13]. While in another study, this regimen could not significantly reduce HBV-DNA levels [11].

Xiao *et al.* [8] did not have HBV-DNA levels in the mothers. Therefore, concluding that hepatitis B had decreased needs more proving data. Furthermore, anti-HBcAb in neonates is an evidence of intrauterine transmission of HBV [14, 15], but in this study it is missing. Passive-active immunoprophylaxis with HBIG and hepatitis B vaccine in the infants of HBV carriers gives high levels of protection against vertical transmission and the rate of infantile infection is uncommon in HBeAg positive and negative mothers [7, 16-19] except in China where rate of transmission is reported to be high [13, 20, 21]. Some infants may be infected intrapartumly or postpartumly and not intrauterinely. It was better to evaluate the cases after completion of postnatal immunoprophylaxis or 12 months after birth [22].

In Xiao *et al.* [8] study the rate of vertical transmission with and without HBIG in mothers was significantly more than that in other reports. Is the mean HBV-DNA level in Chinese women higher than that from other parts of the world? Does genotype of hepatitis possibly B affect the HBV-DNA levels and rate of transmission? If the rate of infection after passive-active immunoprophylaxis in infants and passive immunoprophylaxis in mothers at antepartum period had not decreased to near zero percent, we should consider other interventions after evaluation of failure causes. Some studies in highly viremic HBsAg positive mothers have shown that, reduction of viremia by lamivudine therapy in the last month of pregnancy could effectively and safely reduce the rate of vertical transmission [13, 23].

References

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97-107.
2. Toukan A. Middle East Regional Study Group. Strategy for the control of hepatitis B virus infection in the middle East and North Africa. *Vaccine* 1990; Suppl **8**: S117-S21.
3. Stevens CE, Neurath RA, Beasley RP, Szmuness W. HBeAg and anti-HBs detection by radio-immunoassay: correlation with vertical transmission of hepatitis B virus in Taiwan. *J Med Virol* 1979; **3**: 237-93.
4. Edmunds WJ, Medley GF, Nokes DJ, O'Callaghan CJ, Whittle HC, Hall AJ. Epidemiological patterns of hepatitis B virus (HBV) in highly endemic areas. *Epidemiol Infect* 1996; **117**: 313-25.
5. Vildozola H. Vaccination against Hepatitis B: 20 years later. *Rev Gastroenterol Peru* 2007; **27**: 57-66.
6. Adibi P, Ghassemian R, Alavian SM. Effectiveness of hepatitis B vaccination in children of chronic hepatitis B mothers. *Saudi Med J* 2004; **25**: 1414-18.
7. Kabir A, Alavian SM, Ahanchi N, Malekzadeh R. Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus in infants born to HBsAg positive mothers in comparison with vaccine alone. *Hepatol Res* 2006; **36**: 265-71.
8. Xiao XM, Li AZ, Zhu YK, Miao J. Prevention of vertical hepatitis B transmission by hepatitis B immunoglobulin in the third trimester of pregnancy. *Int J Gynaecol Obstet* 2007; **96**: 167-70.
9. Ranger-Rogez S, Denis F. Hepatitis B mother--to--child transmission. *Expert Rev Anti Infect Ther* 2004; **2**: 133-45.
10. Xiao-Mao L. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. *World J Gastroenterol* 2004; **21**: 3215-7.
11. Yuan J, Lin J, Xu A, Li H, Hu B, Chen J, *et al.* Antepartum immunoprophylaxis of three doses of hepatitis B immunoglobulin is not effective: a single-centre randomized study. *J Viral Hepat* 2006; **13**: 597-604.
12. Ngui SL, Andrews NJ, Underhill GS, Heptonstall J, Teo CG. Failed postnatal immunoprophylaxis for hepatitis B: characteristics of maternal hepatitis B virus as risk factor. *Clin Infect Dis* 1998; **27**: 100-6.
13. Li XM, Yang YB, Hou HY, Shi ZJ, Shen HM, Teng BO, *et al.* Interruption of HBV intrauterine transmission: A clinical study. *World J Gastroenterol* 2003; **9**: 1501-3.
14. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Vimolkej L, Yano M. Is there evidence for intrauterine HBV infection in newborns of hepatitis B carrier mothers? *Southeast Asian J Trop Med Public Health* 1997; **28**: 365-9.
15. Rumi MA, Begum K, Hassan MS, Hasan SM, Azam MG, Hasan KM, *et al.* Detection of hepatitis B surface antigen

in pregnant women attending a public hospital for delivery: implication for vaccination strategy in Bangladesh. *Am J Trop Med Hyg* 1998; **59**: 318-22.
16. Poovorawan Y, Sanpavat S, Pongpunglert W, Chumdermpadetsuk S, Sentrakul P, Vandepapeliere P, *et al*. Long term efficacy of hepatitis B vaccine in infants born to hepatitis Be antigen-positive mothers. *Pediatr Infect Dis J* 1992; **11**: 816-21.
17. Tang JR, Hsu HY, Lin HH, Ni YH, Chang MH. Hepatitis B surface antigenemia at birth: a long-term follow-up study. *J Pediatr* 1998; **133**: 374-7.
18. Hieu NT, Kim KH, Janowicz Z, Timmermans I. Comparative efficacy, safety and immunogenicity of Hepavax-Gene and Engerix-B, recombinant hepatitis B vaccines, in infants born to HBsAg and HBeAg positive mothers in Vietnam: an assessment at 2 years. *Vaccine* 2002; **20**: 1803-8.
19. Noto H, Terao T, Ryou S, Hirose Y, Yoshida T, Ookubo H, *et al*. Special Committee for Preventing Hepatitis B in Shizuoka. Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus carrier state in Shizuoka, Japan during 1980-1994. *J Gastroenterol Hepatol* 2003; **18**: 943-9.
20. Zhu Q, Lu Q, Gu X, Xu H, Duan S. A preliminary study on interruption of HBV transmission in uterus. *Chin Med J* (Engl) 1997; **110**: 145-7.
21. Li C. Clinical observation on interruption of intrauterine transmission of HBV by HBIG. *Chin J Clin Hepatol* 2004; **20**: 196.
22. Poland GA, Jacobson RM. Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* 2004; **351**: 2832-8.
23. 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**: 294-7.