CLINICAL—LIVER

Effects of Maternal Screening and Universal Immunization to Prevent Mother-to-Infant Transmission of HBV

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See Covering the Cover synopsis on page 681.

BACKGROUND & AIMS: Mother-to-infant transmission is the major cause of hepatitis B virus (HBV) infection among immunized children. There has been much debate about screening pregnant women and administering hepatitis B immunoglobulin (HBIG) to newborns. We analyzed the rate of HBV infection among children born to hepatitis B surface antigen (HBsAg)-positive mothers and whether HBIG administration reduces transmission. **METHODS:** We analyzed data from 2356 children born to HBsAg-positive mothers, identified through prenatal maternal screens. In addition to HBV vaccines, HBIG was given to all 583 children with hepatitis B e antigen (HBeAg)-positive mothers and to 723 of 1773 children with HBeAg-negative mothers. Serology tests for HBV were performed from 2007 to 2009, when children were 0.5–10 years old. **RESULTS:** A significantly greater percentage of children with HBeAg-positive mothers tested positive for antibodies against the hepatitis B core protein (16.76%) and HBsAg (9.26%) than children with HBeAg-negative mothers (1.58% and 0.29%, respectively; $P <$ .0001 and $<$.001). Among the HBV-infected children, the rate of chronicity also was higher among children with HBeAg-positive mothers than children with HBeAg-negative mothers (54% vs 17%; $P = .002$). Similar rates of antibodies against the hepatitis B core protein (0.99% and 1.88%; $P = .19$) and HBsAg (0.14% and 0.29%; $P = .65$) were noted in children born to HBeAg-negative mothers who were or were not given HBIG. Infantile fulminant hepatitis developed in 1 of 1050 children who did not receive HBIG (.095%). **CONCLUSIONS: Children born to HBeAg-positive mothers are at greatest risk for chronic HBV infection (9.26%), despite immunization. Administration of HBIG to infants born to HBeAg-negative mothers did not appear to reduce the rate of chronic HBV infection, but might prevent infantile fulminant hepatitis. Screening pregnant women for HBsAg and HBeAg might control mother-to-infant transmission of HBV.**

Keywords: Vaccination; Screening Pregnant Women; HBsAg Carrier; Pediatric Liver Disease.

Hepatitis B virus (HBV) infection is a worldwide health problem, with approximately 360 million people chronically affected and 1 million deaths each year attributed to HBV.[1,2] Because of the high rate of mother-to-infant transmission of HBV, and because of the highest chronic infection rate and the risks of developing hepatocellular carcinoma (HCC) among subjects who are infected early in life, the immunization of newborns has been proven to be the most effective way of reducing chronic HBV carrier rates and HCC in the population.[2–9] The World Health Organization has integrated HBV immunization into the Expanded Program on Immunization. By 2008, 177 countries had introduced hepatitis B vaccination into their national immunization programs.[10]

Despite the significant reduction of HBV carrier rate and HCC after universal infant immunization, we should be aware of the fact that current immunoprophylaxis cannot eradicate mother-to-infant HBV transmission completely. Neonatal immunization may result in a 75% to 90% reduction of the carrier rate, with active immunization (vaccines) alone or active plus

Abbreviations used in this paper: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HCC, hepatocellular carcinoma.

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passive immunization (ie, hepatitis B immunoglobulin [HBIG]) at birth.[5–8,11] At least 10% of the cases of HBV transmission cannot be prevented by immunization. Moreover, children with breakthrough HBV infection have a higher risk of developing HCC, compared with nonvaccinated HBV carrier children.[12] Fulminant hepatitis may develop in infants born to hepatitis B e antigen (HBeAg)-negative, hepatitis B surface antigen (HBsAg)-carrier mothers despite immunization.[13–16] We have shown in a population-based study that 88% of the children with breakthrough infection had HBsAg-positive mothers,[17] indicating that maternal-infant transmission is the major source of HBV infection in the postimmunization era. Although there were previous reports of breakthrough infection rates in immunized infants born to HBeAg-positive mothers, those data were mostly from small-scale studies or performed in the 1980s when universal vaccination had just began.[6,11,18–20] There have been no clear large-scale data from the universal vaccinated population regarding the rate of breakthrough infection among children with HBV-carrier mothers, and there especially are a lack of data on the different infection rates in those born to HBeAg-negative vs HBeAg-positive mothers.

Currently, there are 3 main strategies of universal immunoprophylaxis against HBV infection, including active immunization only (such as in Thailand), active immunization of all newborns plus passive immunization (ie, HBIG) of neonates born to HBsAg-carrier mothers (such as in the United States), and active immunization of all newborns plus passive immunization of neonates born to HBsAg- and HBeAg-positive mothers (such as in Taiwan).[2,3,21,22] In the latter 2 strategies, the screening of pregnant women for HBsAg and/or for HBeAg is required. However, these policies have been based on previous small-scale vaccine trials conducted mostly in children born to HBsAg- and HBeAg-positive mothers.[6,7,23] A controversy exists as to whether to give or not to give HBIG at birth to neonates born to HBeAg-negative, HBsAg-carrier mothers, owing to a lack of convincing evidence comparing the breakthrough HBV infection rate and immunization efficacy in this group with or without HBIG at birth. These data are of great importance in helping to determine the government's strategy for screening pregnant women, administering the neonatal HBV vaccines and the HBIG program, and surveillance of high-risk children in the immunized population.

A universal HBV immunization program was launched in Taiwan in July 1984, making it one of the first programs in the world. A significant decrease in the chronic HBV carrier rate in the population, from 10%–20% to 1%–2%, a reduction in the incidence of HCC by two thirds, and a decreased incidence of infantile fulminant hepatitis, have been observed.[4,12,17,24–28] The program entails that HBV vaccines be given to all newborns and that HBIG be given only to those born to HBeAg-positive, HBsAg-carrier mothers.[18,28] In the past 10 years, a growing number of parents have chosen to administer self-paid HBIG to their newborns born to HBeAg-negative, HBsAg-carrier mothers, despite no solid data pointing to the benefit of HBIG for this group. In recent years, many medical professionals and parents strongly urged administering HBIG to children born to HBeAg-negative mothers, as per US guidelines. This study then was conveyed under the request of the Center of Disease Control, Department of Health of Taiwan, to seek evidence supporting a change of the national program.

Immunized children with breakthrough HBV infection comprise a population of chronic liver disease patients who have a higher risk of developing HCC than the HBsAg-carrier children born in the pre-immunization era.[12] This population has been overlooked, and this problem hinders the success of eradicating HBV infection. Recently, new insights into interrupting such maternal-infant transmission have been reported using nucleoside analogs to reduce maternal viral load during the last trimester of pregnancy.[29,30] Chronic HBV infection in pregnant women, as it pertains to maternal and child health, is an issue attracting growing attention but with many unresolved problems.[31,32] In this study, we conducted a multicenter survey of children born to HBsAg-carrier mothers. Based on our particular universal HBsAg/HBeAg screening program for pregnant women that has been applied only in a small number of countries, we were able to accurately define prenatal maternal HBeAg positivity, and to determine the breakthrough infection rates of children born to HBsAg-carrier mothers, with respect to the maternal HBeAg status in a large population.

Materials and Methods

Universal Immunization Program

The universal HBV immunization program in Taiwan was implemented in July 1984. During the first 2 years (July 1984 to June 1986), only children of HBsAg carrier mothers were covered by the immunization program. Plasma-derived vaccines were used before July 1992 and thereafter were shifted to 3-dose recombinant vaccines (administered at 0, 1, and 6 months). HBIG is administered within 24 hours after birth to newborns born to HBeAg-positive, HBsAg-carrier mothers.[17,18,24,28] The option of receiving self-paid HBIG for infants born to HBeAg-negative, HBsAg-carrier mothers is provided in most hospitals. The national HBV vaccine coverage rate of 3 or more doses in infants was higher than 92%.[4]

Study Design and Population

A total of 9177 children born to HBsAg-positive mothers delivered in 9 tertiary referral hospitals in northern, central, and southern Taiwan from 1996 to 2008 were invited to join this study. Children born with a gestational age of 35 weeks or younger, with a body weight of 2300 g or less, or with apparent birth defects were excluded. Among them, 2379 agreed to participate in the study with parental consent. Blood sampling was performed once for each subject from January 2007 to January 2009, when children were at a chronologic age of 6 months to 10 years (Figure 1).

Maternal serum HBsAg and HBeAg levels were tested in the third trimester of pregnancy and recorded in the charts of mothers and newborns according to the national screening program for pregnant mothers. A computerized national registration system for maternal HBsAg and HBeAg status and for infant immunization records in the Department of Health was