Perinatal Transmission of Hepatitis B Virus in Thailand*

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SUMMARY Perinatal transmission of hepatitis B virus (HBV) from asymptomatic HBsAg carrier mothers to their infants was studied in 78 mother-infant pairs by determination of HBsAg, HBeAg and anti-HBe both in the mothers and in their infants at regular intervals for those children up to the time when they reached at least one year of age. Twenty-five out of the 78 (32.1%) infants born to these mothers were HBsAg-positive 2-6 months after birth and they remained so throughout the observation period of at least one year or more. Perinatal HBV transmission occurred only in infants born to HBsAg carrier mothers who were HBeAg-positive (92.6%) but not in those born to HBsAg carrier mothers who had no detectable HBeAg. This study suggests that preventive measures againt HBV transmission during the perinatal period should be taken only for infants born to HBsAg carrier mothers who are HBeAg-positive.

In addition, the active immune response to HBV was studied in 75 non-HBsAg carrier infants born to HBsAg carrier mothers by determination tion of anti-HBs at one year of age or older. Forty-three of these infants were treated with HBIG at birth and 32 infants received no treatment. It was found that infants born to HBsAg carrier mothers who were HBeAg-positive had a better active immune response (84.2% positive for anti-HBs) than infants born to HBsAg carrier mothers who had no detectable HBeAg or anti-HBe (14.3% and 20.4% positive for anti-HBs respectively).

ASIAN PACIFIC J ALLERG IMMUN 1985; 3:191-193.

Hepatitis B virus (HBV) infection and chronic carriers of the virus are common in all Asian countries. There is non-substantial evidence that chronic infection with HBV is aetiologically associated with the development of primary hepatocellular carcinoma (PHC).[1,2] In areas where HBV is endemic, PHC is one of the most commonly found malignant tumours. In a study in Taiwan of chronic HBV carriers and controls, the relative risk of PHC in carriers was over 200 times that of non-carriers.[3] More than 95 per cent of the PHC cases have developed in chronic carriers.[3,4] In our study in Thailand we found that maternal transmission plays a major role in the transmission of HBV and in the development of the HBV carrier state in their children.[5] Carrier mothers who are also HBeAg-positive are more likely to transmit HBV to their newborn infants than those who are anti-HBe-positive or do not have either of the HBeAg markers.[6,7] Infection at an early age, particularly maternally transmitted infection, may increase the risk of development of chronic liver disease and PHC, and decrease the age of onset of those diseases.[2] Hence, the mother-child relationship in HBV transmission is obviously important with respect to the pathogenesis of chronic liver disease and PHC. Also, it is important in the development of methods for the control of infection, particularly the use of the recently available hepatitis B immunoglobulin and hepatitis B vaccine. We report a prospective study of mother-child HBV relationships conducted at Siriraj Hospital, during a five-year period.

MATERIALS AND METHODS

From September 1978 to September 1983, seventy-eight pairs of asymptomatic pregnant carriers of HBsAg and their infants were selected for a prospective study of perinatal HBV transmission. Initial screening of pregnant women for HBsAg, HBeAg and anti-HBe was done in the prenatal clinic by reverse passive haemagglutination (RPHA) and passive haemagglutination (PHA) tests respectively, as

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previously described.[9] Infants born to those mothers were examined at birth, and at 2, 4, 6 and 12 months of age for clinical evidence of hepatitis and laboratory determinations of serum HBsAg, HBeAg and anti-HBe. The infants' specimens were tested for HBsAg by enzyme linked immunosorbent assay (ELISA, using a Behring-Enzygnost® HBsAg test kit). The HBeAg and anti-HBe tests were performed by RPHA and PHA (anti-e cell Neo and e-cell Neo, Green Cross Co., Japan). None of the infants had any treatment for the prophylaxis of HBV transmission and all of them had been followed up regularly for at least one year after birth.

In order to study the immune response of the non-HBsAg carrier infants in relation to the HBsAg carrier status of their mothers, another 75 infants born to HBsAg carrier mothers but who became non-HBsAg carriers at one year or more of age were included in this study. In this group of infants, 43 were treated with hepatitis B immune globulin (HBIG), 1.0 ml intramuscularly within 48 hours of birth, while 32 infants received no treatment. All the infants were examined for HBV markers at the same regular intervals as those in the first group. In addition, anti-HBs was detected by the ELISA method (Behring-Enzygnost,® anti-HBs kit) in the children one year of age or older.

Statistical analysis was evaluated by Chi-square test.

RESULTS

Among the 78 HBsAg carrier mothers in the first group, 25 (32.1%) of the infants born to them were HBsAg positive. In all those infants, the HBsAg appeared during a period of 2 – 6 months after birth, and persisted throughout the observation period of at least one year or more. When the incidence of HBsAg carrier state in the infants was considered in relation to the presence of HBeAg in their mothers, it was found that 27 out of 78 (34.6%) HBsAg carrier mothers had HBeAg in their sera and 19 (24.4%) had anti-HBe, while the rest had neither HBeAg nor anti-HBe. As shown in Table 1, the perinatal transmission of HBsAg from the carrier mothers, which caused the incidence of the persistent HBsAg-carrier states in their infants, was found only in the group of HBsAg-carrier mothers who were HBeAg-positive (92.6%), but not in HBsAg carrier mothers who had no detectable HBeAg. This is a statistically significant difference ($p < 0.01$).

Among 75 infants who did not develop persistent antigenaemia (43 in the HBIG treated group and 32 in the untreated group), 27 (36%) developed anti-HBs at one year of age or older (Table 2). When the active immune response in these infants was considered in relation to the HBsAg carrier state of their mothers, it was found that the infants born to HBsAg carrier mothers, who also were HBeAg-positive, had a better active immune response (84.2% positive for anti-HBs) than infants born to HBsAg carrier mothers who had no detectable HBeAg or anti-HBe (14.3% and 20.4% positive for anti-HBs respectively). The incidence of anti-HBs-positive infants born to mothers in the HBeAg-positive group was statistically significantly different ($p < 0.01$) compared with that of the other two groups (Table 2).

DISCUSSION

It is of particular interest that not all the HBsAg carrier mothers transmitted HBV to their offspring even in a geographical area where there is a high rate of maternal transmission. Factors which influence this vertical transmission of HBV from the carrier mothers to their infants have been investigated. Accordingly, the serum samples of mothers "with" and "without" perinatal transmission were studied immunologically; titres of HBsAg and its subtypes, titres of anti-HBc

Table 1 Perinatal transmission of hepatitis B surface antigen (HBsAg) and e-antigen (HBeAg) from HBsAg carrier mothers to children at one year of age.

Group of mothers with			No.	No. positive in infants		
HBsAg	HBeAg	anti HBe	test	HBsAg	HBeAg	anti HBe
+	+	–	27	25 (92.6%)	20 (74.1%)	0
+	–	+	19	0	0	0
+	–	–	32	0	0	0
Total			78	25 (32.1%)	20 (25.6%)	0

Table 2 Incidence of anti-HBs at one year or more of age in 75 non-HBsAg carriers born to HBsAg carrier mothers

Group of mothers with			No.	No. of anti-HBs positive infants
HBsAg	HBeAg	anti HBe	test	
+	+	–	19	16 (84.2%)
+	–	+	7	1 (14.3%)
+	–	–	49	10 (20.4%)
Total			75	27 (36%)

and the presence of HBeAg or anti-HBe were determined and compared. There was a definite difference in the serum samples of mothers who transmitted HBV and those who did not.[8,9]

In the present study, it was found that perinatal infection of infants by mothers who were HBsAg-positive was most likely to occur when the mothers were also HBeAg-positive. Thus, about 90 per cent of infants whose mothers are positive for both markers may be expected to become infected and almost all of them will become permanent carriers. Infants born to mothers who are HBeAg-negative or who have antibody to HBeAg are at lesser risk, but can still become infected.[7] However, our study showed clear-cut evidence that HBV transmission does not occur during the perinatal period of infants born to HBsAg carrier mothers who are HBeAg-negative. This study indicates that the high incidence of perinatal HBV transmission (32.1%) for HBsAg carrier mothers to their infants is due to the high incidence of HBeAg (34.6%) among pregnant HBsAg carrier women in Thailand. By contrast, a report from Africa shows that only 19.8 per cent of HBsAg carrier mothers were HBeAg-positive and the HBV infections did not occur perinatally, but did occur at a high rate of incidence later in infancy and childhood.[10]

Long-term follow-up of the group of Thai children is in progress to determine the incidence of additional HBsAg carriers resulting from horizontal transmission later in infancy and childhood. The result of the present study also indicates that preventive measures to protect against HBV transmission during the perinatal period should be taken only for infants born to HBsAg carrier mothers who are HBeAg-positive. Our previous study has shown that hepatitis B immune globulin (HBIG) given to newborn babies is able to reduce the rate of HBV transmission from HBsAg carrier mothers to their infants from 85.7% to only 26.3%.[5] The result of our anti-HBs study (Table 2) indicates that the risk of continued exposure is not as high as we formerly thought because most of the non-HBsAg infants born to HBeAg-positive mothers have a much better active immune response than infants and children in the other groups with a statistically significant difference ($P < 0.01$).

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