VERTICAL TRANSMISSION OF THE HEPATITIS B SURFACE ANTIGEN IN THAILAND

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INTRODUCTION

Hepatitis B antigen (HBAg) is associated with hepatitis B virus infection (Blumberg *et al.*, 1970; Krugman *et al.*, 1970). Acute hepatitis, chronic forms of hepatitis, cirrhosis and malignant hepatoma may occur in some individuals infected by this virus (Blumberg *et al.*, 1970; Tong *et al.*, 1971; Obayashi *et al.*, 1972; Chaiyanuvati *et al.*, 1975). Carrier rates are particularly high in tropical and subtropical countries (Blumberg *et al.*, 1970). In Thailand, the carrier rates have been reported to be 8% to 10% (Punyagupta *et al.*, 1973 Pongpipat *et al.*, 1979). Vertical transmission implies transmission of the hepatitis B virus from mothers to their infants. This occurs with great frequency (70 - 100 %) when the mother has acute hepatitis near delivery (Schweitzer, 1975). However, the rate of transmission of the hepatitis B surface antigen (HBsAg) from asymptomatic carrier mothers to their infants varies from 0 to 72 % in different parts of the world. A compilation of six prospective studies from the United States and Europe showed only 3 % to 7 % transmission from asymptomatic carrier mothers (Schweitzer *et al.*, 1973; Papaevangelou *et al.*, 1974; Fawaz *et al.*, 1975; Skinhoj *et al.*, 1976) ; but the Japanese investigators have shown maternal carrier to infant transmission rate to be as high as 72% (Okada *et al.*, 1975, 1976). Similarly, a prospective study of pregnant HBsAg carriers in Taiwan demonstrated transmission of HBsAg to 63 % of the resulting infants (Anderson *et al.*, 1975). In Pakistan (Aziz *et al.*, 1973) and Thailand (Punyagupta *et al.*, 1973), lower rates of vertical transmission were observed as compared to Japan and Taiwan. Since Thailand is an endemic area with high incidence of HBsAg carriers (Punyagupta *et al.*, 1973; Pongpipat *et al.*, 1979), our study was designed to reinvestigate the rate of HBsAg transmission from Thai pregnant women to their infants, as well as to determine whether or not the new antigen system, the HBeAg and its antibody, influence the rate of transmission.

MATERIALS AND METHODS

From September 1978 to April 1979, 2380 pregnant women aged 16-40 years from the prenatal clinic of Siriraj Hospital were screened for HBsAg in their sera. The HBsAg carriers were detected in 110 out of 2380 (4.6%) pregnant women. Asymptomatic pregnant carriers of HBsAg were selected for further study of vertical transmission by the following criteria: (1) the presence of HBsAg in their sera throughout the observation period of 6 months or more; (2) absence of clinical evidence of liver disease; (3) no laboratory abnormalities in measurement of liver function (serum glutamic oxaloacetic transaminase activity). Forty-two pairs of asymptomatic HBsAg carrier mothers and their infants were examined at least once a month after delivery for clinical evidence of hepatitis and laboratory determinations of serum HBsAg, HBeAg, HBeAb, and liver function (SGOT). The period of follow up was at least six months to one year. In addition, thirty-four fathers and 27 siblings aged under 5 years of these

pregnant carriers of HBsAg were also similarly studied. The HBsAg was detected by counter immuno-electrophoresis (CEP) as previously described (Pongpipat *et al.*, 1971). The HBeAg and HBeAb were determined by agarose gel diffusion after the serum was five times concentrated by lyphogel before testing. Details of the laboratory procedures used for HBeAg and HBeAb detection have been published elsewhere (Pongpipat *et al.*, 1979).

RESULTS

Among 42 HBsAg carrier mothers, 13 (30.9 %) infants born from these mothers had HBsAg positive (Table 1). In all 13 infants, the HBsAg appeared during 3 to 6 months after delivery; and persisted throughout the observation period of one year. There were neither congenital malformations nor clinical evidence of hepatitis apparent at routine postnatal and the follow up examination in these infants. All infants were thriving without clinical or laboratory evidence of hepatitic disease during the period of observation despite persistent antigenemia. Among 42 HBsAg carrier mothers, 17 (40.5 %) had HBeAg positive in their sera and 8 (19 %) had HBeAb, while the rest had neither HBeAg nor HBeAb. To evaluate the influence of e-antigen-anti-e system on the rate of maternal-infant transmission, the incidence of vertical transmission was expressed as the percentage of HBsAg carrier babies found from HBsAg carrier mothers with HBeAg, with HBeAb antibody or without both HBeAg and HBeAb. As shown in table 1, the vertical transmission of HBsAg from the carrier mothers to their infants was found in only the group of HBsAg carrier mother who had HBeAg positive (76.5 %) but none in HBsAg carrier mother who had no detectable HBeAg which is statistically significant ($p<0.05$). Similarly, vertical transmission of HBsAg from HBsAg carrier mothers to other siblings (under 5 years of age) occurred in 8 out of 9 children from those mothers with HBeAg positive but only 2 out of 18 children from those mothers with HBeAg negative which also shows statistically significant difference ($p<0.05$). Most of the HBsAg carrier babies (70.5 %) and siblings (77.7 %) from mothers with HBeAg positive group also had HBeAg in their sera. None of the infants born from HBsAg carrier mothers

Table 1

Vertical transmission of hepatitis B surface antigen (HBsAg) and e-antigen (HBeAg) from HBsAg carrier mothers to their infants and children (under 5 years of age)

Group of Mothers with			No.	No. positive in Infant			No.	No. positive in Siblings		
HBsAg	HBeAg	HBeAb*	Test	HBsAg	HBeAg	HBeAb	Test	HBsAg	HBeAg	HBe Ab
+	+	–	17	13 (76.5%)	12 (70.5%)	0	9	8 (88.9%)	7 (77.7%)	1 (11.1 %)
+	–	+	8	0	0	0	4	0	0	0
+	–	–	17	0	0	0	14	2	1	0
Total			42	13 (30.9%)	12 (28.6%)	0	27	10 (37%)	8 (29.6%)	1 (3.7%)

* HBeAb = anti-e antibody, + = positive, – = negative

developed HBeAb while only one out of 27 other siblings had HBeAb. Fig. 1 illustrates the correlation of HBeAg positivity and HBsAg titer in carrier mothers, their infants and children. It can be seen that the majority of both HBsAg carrier mothers and their children who had HBeAg positive had high HBsAg titer.

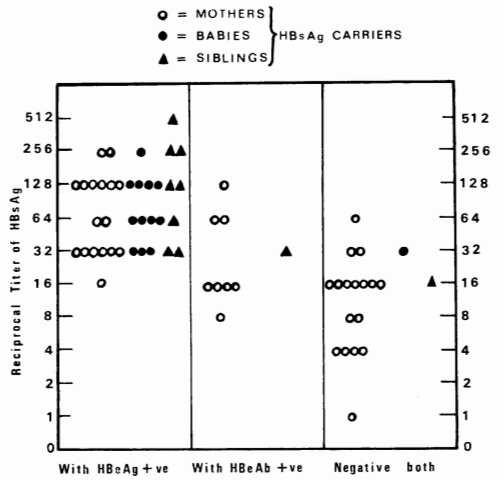

Fig. 1—Correlation of the presence of the e-antigen (HBeAg) or anti-e antibody (HBeAb) with the titer of hepatitis B surface antigen (HBsAg) in 42 HBsAg carrier mothers, 13 babies and 10 siblings.

Study on 34 fathers of these families revealed that only 3 fathers had HBsAg positive. One of the HBsAg carrier father had HBeAg and another had HBeAb while the other one had neither HBeAg nor HBeAb.

DISCUSSION

Vertical transmission of HBV from asymtomatic chronic carrier mother to her infant is considered to be an important factor for the prevalence of HBsAg carriers in infants and children (Schweitzer *et al.*, 1975; Isenberg, 1977). In this study the vertical transmission of the HBsAg from asymtomatic HBsAg carrier pregnant women to their babies was as high as 30.9 %. This result is in contrast to the previous study in this country which revealed no vertical transmission at all (Punyagupta *et al.*, 1973). This discrepancy may be due to the small number (only 14 mother-infant pairs) of case studies, shorter duration of follow up (only 6 months after birth) and less sensitive method (immunodiffusion) used for the detection of HBsAg in the previous study. In other published reports from different parts of the world, the rate of vertical transmission was variable. It is of general agreement that vertical transmission occurs in a low rate (0 to 7 %) where the incidence of HBsAg carriers in the population is low such as in Europe and United States (Schweitzer *et al.*, 1972; Papaevangelou *et al.*, 1974, Skinhoj *et al.*, 1976). However, reports from areas of the world with high endemic rates of the chronic HBsAg carrier state (Taiwan and Japan) have indicated higher rates of transmission from 40 to 72 % (Ohbayashi *et al.*, 1972; Okada *et al.*, 1975; Anderson *et al.*, 1975). Thailand is also a high endemic area with the carriers rate of HBsAg being 8-10 % (Pongpipat *et al.*, 1979; Punyagupta *et al.*, 1973) which might be one factor accounted for the high incidence of vertical transmission of HBsAg found in the present study. Other factors besides the prevalence of the HBsAg carriers among Thai population probably included the high HBsAg titer in mothers and the presence of HBeAg in the asymptomatic HBsAg carrier mothers. The source of HBsAg which the infants acquired in the neonatal period is most likely to be directly from their mothers. In this study, 13 out of 42 infants became HBsAg positive between 3 and 6 months of age. This incubation period is in agreement with previous works (Okada *et al.*, 1975; Mollica *et al.*, 1979), suggesting that infection with HBV usually takes place during the immediate perinatal period. There is certainly ample opportunity for HBV transmission at or near birth via maternal blood and amniotic fluid and later

by menstrual blood, breast milk and saliva (Schweitzer *et al.*, 1973; Gerety *et al.*, 1977). The result of our study suggested that the transmission of HBsAg to these babies should be directly from the mothers but not from the fathers, since only three out of 34 fathers were found to be HBsAg positive. Therefore fathers were not the important sources of HBV transmission to the babies. Furthermore, one striking finding in our study was the close relationship between HBeAg positivity in the HBsAg carrier Thai mothers and the development of HBsAg positivity in their babies. It was known that the presence of HBeAg in the HBsAg carrier is the index of infectivity of HBV (Alter *et al.*, 1976). In recent studies, the rate of vertical transmission of HBsAg from HBsAg carrier mothers with e-antigenemia to their babies was as high as 85-100 % (Schweitzer *et al.*, 1975; Skinhoj *et al.*, 1976; Okada *et al.*, 1976; Beasley *et al.*, 1977). This rate of transmission is approximately the same with our findings. In our study, vertical transmission of the HBsAg from HBsAg carrier mothers to their infants (76.5%) and other siblings (88.9%) occurred only in those mothers with HBeAg positive but rarely in HBeAg negative mothers. Our studies also demonstrated a good correlation between the presence of HBeAg and a high HBsAg titer in carrier mothers, their babies and siblings. Therefore, high HBsAg titers and HBeAg in our carrier mothers were equally good markers ofHBV infectivity. However, it should be noted that the mothers with high HBsAg titers but no detectable HBeAg did not show vertically transmitted HBV; on the other hand all HBsAg-positive babies had HBeAg positive mothers. In this study, HBeAg was therefore a most perfect predictor of the development of HBsAg persistent antigenemia in the babies. All of the HBsAg positive babies and siblings showed persistent HBsAg antigenemia and e-antigenemia throughout the period of study. Most of these carrier infants are very infective as shown by the high titer of HBsAg and HBeAg in their blood. However none of these HBsAg carrier infants showed clinical manifestation of hepatitis and there is no significant difference between the liver enzyme (SGOT) level between serum samples of infants with HBsAg positive and those with HBsAg negative. Our previous report (Pongpipat *et al.*, 1979) taken together with the present result showed high prevalence rates of HBeAg in asymptomatic HBsAg carriers in Thailand especially in younger age group which is mainly due to vertical transmission from HBsAg carrier mother. We can assume that the vertical transmission of HBV play a major role in acquiring a spectrum of hepatic diseases ranging from all types of hepatitis, cirrhosis and primary liver cancer in adults as previously postulated (Chaiyanuvati *et al.*, 1975). On the basis of these results a strategy is indicated to prevent persistent antigenemia in infant of HBsAg carrier mothers with HBeAg in areas with a high prevalence of HBsAg carriers (Anderson *et al.*, 1975; Mollica *et al.*, 1979). Kohler *et al.*, (1974) and Dosik *et al.*, (1978) have suggested that a chronic HBsAg carrier state in infants might be prevented by the administration of hyperimmune HBsAg globulins in the immediate postnatal period. A control trial of the such passive immunization with hyperimmune HBsAg globulin in selected group of infants born from HBsAg carrier mothers with HBeAg should provide useful information for the large scale prevention and eradication of HBsAg in the hyperendemic area.

SUMMARY

The vertical transmission of the hepatitis B surface antigen (HBsAg) from HBsAg carrier mothers to their infants and children were studied in 42 mother-infant pairs, 27 siblings aged under 5 years and 34 fathers of these families. Thirteen out of 42 (30.9%)

infants born from these mothers became HBsAg carriers at 3 to 6 months of age. Vertical transmission of the HBsAg from HBsAg carrier mothers to their infants (76.5%) and other siblings (88.9%) occurred only in those mothers with e-antigen (HBeAg) positive but none in HBsAg carrier mothers without HBeAg. Most of the HBsAg carrier babies (70.5 %) and their siblings (77.7 %) born from the carrier mothers with HBeAg positive also had HBeAg in their sera. Good correlation of the presence of HBeAg and high titer of HBsAg was found both in HBsAg carrier mothers and in their offsprings. This study clearly shows that HBsAg carrier Thai mothers with HBeAg transmitted hepatitis B virus vertically to their infants and children more readily than do the HBsAg carrier mothers without HBeAg.

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