

MOTHER TO NEWBORN AND INFANT TRANSMISSION OF HEPATITIS B INFECTIONS

V.J.L. HOW. M.B., B.S.*

Summary

A review of maternal transmission of HBV infections revealed that transmission rates are high in many countries in Asia, due mainly to the high prevalence of carriers and high HBeAg rates in these carriers. **Transmission** can occur in the antepartum, intrapartum and postpartum periods. About 90% occurs at the time of birth, and 5-10% are the result of in-utero infection. 90% of newborns infected at this age become chronic carriers. Maternal transmission is responsible for about 40-50% of the pool of carriers in Asia, for clustering of carriers, chronic liver disease and primary hepatocellular carcinoma, and is a continuing source of the virus. The role of the HBeAg, anti-HBe and changing patterns in the ability of infected newborns and young females to respond to HBV infections is also discussed.

INTRODUCTION

The prevalence of the chronic Hepatitis B surface antigen (HBsAg) carrier state shows a marked geographical variation. In the industrialized countries of North America, Australia and Western Europe, less than 1% of the population surveyed were HBsAg reactive. This contrasts sharply with reports from countries in tropical Africa, South East Asia and the Far East where between 5 to 15% of the population are chronic carriers. It is estimated that as many as 215 million people or 5% of the world population are chronic carriers.^{1, 2}

Data from parts of the world with moderate to high carrier rates, such as countries in Asia, indicate that maternal transmission of the Hepatitis B virus (HBV) in these areas may be responsible for a large proportion of the total carrier pool.^{3, 4, 5}

The possibility of maternal transmission of viral hepatitis was first suggested by Stokes et al. in a paper titled "Viral Hepatitis in the Newborn" published in 1951⁶. A carrier state and familial hepatitis was documented by Stokes et al., **Krainin & Lapman** and by **Beard**,^{7, 8, 9} many years before the discovery of the Australia antigen (now referred to as HBsAg) by Blumberg in 1964¹⁰ and the identification of the HBV by Dane in 1970.¹¹

In the years following the discovery and identification of HBV, considerable advances have been made in this area and it is now generally accepted that maternal transmission can occur whenever the mother is infected with HBV in pregnancy. Transmission can therefore occur under 2 separate settings,

firstly, when the mother has acute hepatitis B infection in pregnancy and secondly, when the mother is a chronic, persistent carrier of the virus.

TRANSMISSION DURING ACUTE HEPATITIS B INFECTION IN PREGNANCY

Transmission from a mother with acute hepatitis B infection in pregnancy was first documented by Schweitzer in 1970.¹² He observed 4 mothers who had acute hepatitis B infection at delivery and reported finding HBsAg in the sera of 3 of the newborns. Schweitzer in 1973 and later Tong in 1981 showed that the frequency of transmission from mother to infant was about 75% when acute Hepatitis B occurred during the third trimester of pregnancy. The frequency was only 10% when the mother was acutely infected in the first and second trimesters.^{13, 14}

Transmission from mothers with acute viral hepatitis B in pregnancy is reported to occur frequently in parts of the world where the carrier rates are low but does not appear to be important in areas where HBV infections are highly endemic.

TRANSMISSION FROM CARRIER MOTHERS TO THEIR OFFSPRING

Derso et al.¹⁵ have shown that there is a high rate of HBV infection and persistence of infection in Chinese babies whose mothers were chronic carriers. HBV infection and persistence in babies born of European carriers was much less common. The differences in transmission rates were difficult to explain

*Department of Medical Microbiology, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur, Malaysia (Address for reprint requests).

until 1976 when Skinhoj and Okada separately highlighted the importance of the HBeAg in maternal transmission. Okada studied 23 asymptomatic carrier mothers and their babies. He found HBeAg in 10/23 of the mothers. All 10 babies whose mothers were HBeAg-positive developed persistent antigenaemia. 10 elder siblings of the newborns whose mothers were HBeAg-positive were also asymptomatic carriers of HBV. Dane particles were found in all 6 samples collected from HBsAg-positive and HBeAg-positive mothers.^{16, 17}

Infection in infancy occurs often when the mother is a chronic HBsAg carrier. It occurs most frequently among Asians apparently because of a very high frequency of HBeAg amongst Asian carriers. HBeAg rates in pregnant women in Asia vary from 26% in China, around 30% in Japan, Taiwan, Thailand and Burma, 41% in Korea, 50% in Singapore and 54% in Hong Kong². The presence of HBeAg correlates with a high rate of viral replication, large numbers of infective viral particles and therefore a correspondingly higher risk of transmission of HBV.

TIME OF TRANSMISSION

Transmission from infected mothers to their children can occur in-utero, around the time of birth or in the postpartum period.

In-utero transmission

Chircu,¹⁸ studied 311 mother-infant pairs and showed that the HBV does not usually cross the placental barrier. Genuine transplacental or in-utero transmissions are rare. They are believed to occur in only 5–10% of pregnancies where the mother is a chronic carrier.^{19, 20} It is perhaps fortunate that only so small a proportion of newborns are infected in the antepartum period. As it must be presumed that HBV infections will already be fairly well established in these infants at birth, it is highly unlikely that any form of intervention, whether it be the use of Hepatitis B Immune Globulin (HBIG) or vaccine or any combination of the two, will have any effect in terminating or arresting the infection in this setting.

Transmission around the time of delivery

Transmission from mother to child occurs 90% of the time at or around the time of delivery i.e. connatally. This is suggested by observations that the peak occurrence of HBs antigenaemia is around 3 months, indicating an exposure at or very soon after delivery.³ This fits in well with what is known

about the long incubation period for Hepatitis B infection. This long incubation period means that nearly all cases of HBV infections in newborns resulting from maternal transmission at or soon after birth may be prevented by the use of HBIG, Hepatitis B vaccine or a combination of both, given as soon as possible after delivery.

Postnatal maternal transmission

Maupas²¹ and Beasley²² have shown that the annual incidence of HBV infections in preschool children in Africa and Taiwan is between 5 and 10%. The carrier mother was identified as a major risk factor in the transmission of infections amongst these children. In much of tropical Africa, transmission at the time of birth accounts for only 25% of all infections in children, even when the carrier mother also has detectable HBeAg. In these areas, most children acquire HBV infections in early infancy and childhood, often from their carrier mothers or from carrier siblings and playmates. The mother with active HBV infection is thus a continuing source of HBV for her offspring who escaped infection at the time of delivery.

MECHANISM OF TRANSMISSION AND INFECTION

The precise mechanism of transmission and infection has not yet been clearly established. At various times breast milk, amniotic fluid, and other body fluids have been incriminated. Wong¹⁹ reported finding HBsAg in 72% of expressed breast milk samples tested but could not evaluate the role of breastfeeding in HBV transmission as the number of breastfeeding mothers in her study was too small. Beasley et al.²³ in a study involving 147 Taiwanese babies of carrier mothers could not demonstrate any relationship between breast feeding and the subsequent development of HBs antigenaemia in the babies. Breast fed and artificially fed infants of carrier mothers acquired HBV infections in almost equal numbers. Breast milk obtained from 32 mothers, 10 of whose babies became persistently HBV infected were tested and HBsAg was not detected in any sample. This was very different from Wong's results and may be due to differences in sample collection. Very forceful expression of milk may conceivably result in small amounts of maternal blood escaping from minute breaks in the nipple and contaminating the sample. HBV has been found in high titres only in blood. It has also been reported to be present, though

only in small numbers, in other body fluids, including breast milk, where its presence has been demonstrable only after concentration techniques have been employed.

It seems reasonable therefore to assume that HBV transmission from infected mothers to their newborn babies probably occurs as a result of exposure to maternal blood containing infective viral particles when the placenta separates and shears off during delivery or when bleeding occurs from mucosal tears or **episiotomy** cuts. Any risks posed by breast milk are probably negligible compared with the large amounts of virus in maternal blood that the baby is exposed to during delivery. It is therefore difficult to justify advising carrier mothers not to breast feed their babies.

OUTCOME OF MATERNAL-NEWBORN TRANSMISSION

HBV infections in the newborn can lead to the following:—

1. *Acute icteric/anicteric hepatitis* followed by recovery and anti-HBs production. Newborns are particularly vulnerable to HBV as they have not yet achieved immunological maturity. Thus less than 5% of infected newborns will manage to eliminate HBV and produce anti-HBs.
2. *Fulminant hepatitis*. Fatal fulminant hepatic failure has been described by Fawaz et al., Ewing & Davidson and other.^{24, 25}
3. *Subclinical infections leading to development of a chronic carrier state* is the most common outcome of congenital HBV infections. Age is a major factor determining the outcome of HBV infections. 20–30% of older children and 5–10% of immunocompetent adults will remain persistently infected but without prophylaxis, more than 90% of newborns infected at birth will become chronic carriers.

Serious chronic liver disease often develops in these young carriers. Wright et al.²⁶ and Shinozaki et al.²⁷ have described chronic active hepatitis and cirrhosis in 9 and 10 month old infants who were infected at birth by their carrier mothers. Primary hepatocellular carcinoma (PHC) in young children has been reported.^{28, 29} Beasley et al.²⁸ documented PHC in a 7 year child who was infected by his carrier mother at birth.

FAMILIAL CLUSTERING OF CARRIERS AND PHC CASES

In 1972, Ohbayashi et al.³⁰ confirmed the importance of the maternal carrier when they documented clustering of HBsAg carriers, chronic liver disease and PHC in families all of whom had mothers who were chronic carriers. Mazzur³¹ studied HBsAg subtypes in families with more than one carrier member. He found that in families where the mother was a carrier, nearly all the children who had chronic antigenaemia shared the same subtype as the mother, suggesting that all infections had come from one common source i.e. the mother. In contrast, in family clusters where the mother was not a carrier, family members shared a variety of different subtypes, evidence against common source infections.

Furthermore, there is a high frequency of HBsAg positivity in mothers and family members of PHC patients. A case control study of PHC family members by Larouze et al.³² found that 71% of mothers of PHC patients were carriers.

It therefore appears that the maternal HBsAg status was largely responsible for family clusters of carriers, of chronic liver disease and PHC.

ANTI-HBe AND MATERNAL HBV TRANSMISSION

Mounting evidence has shown that the risk to infants whose mothers were either HBeAg-negative or anti-HBe-positive is not as negligible as was previously assumed. Anti-HBe-positive mothers were once believed to carry almost no infective viral particles and thus pose little risk to their offspring. The less sensitive tests used previously only detected little or no HBV in anti-HBe-positive carriers but newer tests utilising hybridisation techniques to detect HBV-DNA polymerase (a good indicator of active viral replication) show that as many as 50% of anti-HBe-positive carriers have detectable HBV-DNA polymerase. Some workers have reported fatal hepatitis B in babies whose mothers were both HBsAg-positive and anti-HBe-positive.^{25, 33, 34}

More data is accumulating rapidly in this area and the current recommendation for prophylaxis is to give HBIG and vaccine to all babies of carrier mothers irregardless of HBeAg status. This would be the ideal practice if funds are available, but it may be difficult to achieve in developing countries where cost is a major constraint. In countries where only limited public funds may be available, an

acceptable compromise would be to give vaccine only to babies of HBeAg-negative mothers and both HBIG and vaccine to babies of HBeAg-positive mothers as soon as possible after birth.

CHANGING MATERNAL HBeAg STATUS AND NEONATAL RESPONSES

Early reports suggested that environment and nutrition played unimportant roles in determining the outcome of infections. Studies conducted in children of immigrants who had migrated from areas of high endemicity to geographical areas where the carrier rates were low showed that the birthplace did not appear to influence the development of a carrier state. First generation migrants and their offsprings who were born in areas of low prevalence shared equally high carrier rates. However, recent studies from Japan and USA show that this may be changing. Obayashi et al.³⁰ have demonstrated that up until the third generation, transmission occurred frequently from mother to infant but the sera of children born to third generation carrier mothers were often HBsAg-negative. Although HBV infections did occur in these children, they seemed able to clear HBV and recover. Anti-HBs became detectable after 2–6 months.

In a survey of antenatal women carried out between 1978–1981 in Yokohama city, Japan, the carrier rate was constant between 1.8% and 2.1% but the HBeAg reactive rate had dropped from 20.8% in 1978 to 9.0% in 1983.³⁵ This downward trend has been attributed to various factors but mainly to better nutrition of the population in Japan. A documented increase in the protein uptake of the Japanese may have helped to improve the immunocompetency of carrier women thus helping them convert naturally from HBeAg-positive to HBeAg-negative status before reaching reproductive age. This decline in the HBeAg rates amongst female carriers will mean that less transmission from carrier mother to newborn will occur.

Tong and colleagues have also been able to show that though children in the first, second and third generations of immigrants from countries where HBV infections are endemic share the same carrier rates as their counterparts in their native countries, offspring of carriers in subsequent generations in Los Angeles, unlike the fourth generation Japanese, also have better ability to eliminate HBV infection. Much lower carrier rates have been observed in these children.³⁶ Again the reasons for this are not clear. This area certainly

deserves further investigation. It may well be that environment and nutrition play more important roles in transmission and persistence of infection than were previously thought. Genetic factors may perhaps be less important.

THE CENTRAL ROLE OF THE HBsAg POSITIVE MOTHER

The mother who is a chronic carrier of HBsAg, particularly if she is also HBeAg-positive, may set in motion a series of events with tragic consequences. The majority of her offspring will become carriers, with associated morbidity and mortality as a result of hepatitis B related chronic liver disease and PHC. Male offsprings may transmit the infection to their wives and children whereas female offsprings, on growing up to become mothers, will in turn transmit HBV to their children and continue the self perpetuating cycle.

The available data indicate that transmission from the carrier mother to the newborn, whether this takes place in the antepartum, intrapartum or postpartum period, is largely responsible for a significant proportion of the world's pool of 215 million chronic carriers. The carrier mother, by continually infecting her offspring is responsible for the familial clustering of chronic liver disease, PHC and chronic carriers. Maternal transmission is probably also responsible for the wide variation in carrier rates observed in different parts of the world, and for differences noted between different ethnic groups in the same area. Preventing transmission of HBV from carrier mothers to neonates will undoubtedly contribute to elimination of the reservoir of virus, to a reduction of the pool of chronic carriers and eventually to a decreased prevalence of PHC and HBV related chronic liver disease.

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