VERTICAL TRANSMISSION OF HEPATITIS B

ELIZABETH H. BOXALL, BSc, PhD
Principal Virologist, Regional Virus Laboratory, East Birmingham Hospital, Birmingham

INTRODUCTION

Vertical transmission can be defined as direct transfer of an infection from the mother to her infant, in utero, or in the perinatal period. Due to the "immunological immaturity" of the foetus and the newborn, there is the possibility that an infection acquired in this way could result in a tolerant state in which the infant becomes a chronic carrier which could result in developmental retardation, recurrent bouts of acute illness, or severe chronic disease later in life. Infections such as hepatitis B which can be spread by contact with an acute case and contact with carriers could be controlled by vaccination of the non-immune, but also by studying methods which may reduce the total number of carriers in a population, or by preventing the initial establishment of the carrier state. To discuss vertical transmission of hepatitis B, transmission from carrier mother must be considered separately from the mother who has acute hepatitis B during her pregnancy.

Acute hepatitis B in pregnancy

The work of Schweitzer (1975a) clearly showed that the risk to the infant is greater if the time of onset of the infection is close to the time of delivery. If the onset of the acute infection is early in pregnancy, there is sufficient time for a full clinical and virological recovery before delivery. If the onset is later, antigenaemia at the time of delivery is likely, and there is a greater chance that the virus will have a higher infectivity as indicated by the presence of e antigen. Some of the babies who have acquired the HBsAg carrier state

in this way have histological evidence of chronic persistent hepatitis. Acute hepatitis in pregnancy is uncommon. In the West Midlands Region over a period of four years, I observed seven clinical and five subclinical case (i.e. one clinical case in every 45,000 pregnancies). The subclinical and early cases did not result in any infection in the babies. In one case where the acute hepatitis probably resulted in a premature delivery at 32 weeks, the baby was immediately transferred to an incubator and was separated from the mother who was clinically unwell. This baby was given divided doses of hyperimmune hepatitis B immunoglobulin in divided doses over six months (table 1). By the time the mother had recovered clinically, the baby had had several doses of immunoglobulin; on follow-up, the baby remained HBsAg negative as did his mother.

Another case where we did not achieve such success was where the mother developed acute hepatitis B one month after delivery. By this time, the baby was producing her own HBsAg, and although immunoglobulin was given, it did not prove effective in eliminating the infection, and it is doubtful whether an even more intensive course at this stage would have been more effective. This child is now a high titre chronic carrier with persistently abnormal liver function tests and histological evidence of chronic persistent hepatitis.

Carrier mothers

Studies into vertical transmission in different parts of the world have produced widely different results. Two distinct groups emerge: in the Western World where the carrier prevalence is low, very few babies become infected, whereas in areas with a high carrier prevalence, particularly in the Far East, a high proportion of babies born to carrier mothers also become carriers (figures varying between 40 and 70%). Our own study of a mixed population within the West Midlands (Derso *et al.*, 1978), showed that the transmission of the carrier state varied with the ethnic origin of the mother (table 2). In our own study, we obtained samples from the babies, at birth, six weeks, four, eight and twelve months. Those babies who became carriers developed an HBs antigenaemia at about three to four months, the development of which was independent of the HBsAg status at birth or the particular feeding method. Our study showed that the children were healthy and thriving, and that there was no evidence that hepatitis B was associated with an unusually high level of abortions, miscarriages, congenital abnormalities or mental or physical retardation of any sort. However, some of the infants who have become HBsAg carriers have abnormally raised transaminase enzymes (table 3). Of seventeen babies in our study, nine have normal enzymes and eight have abnormal values

Table 1. — *Prevention of Hepatitis B carrier state in infants by use of hyperimmune Hepatitis B immunoglobulin.*

Dosage regimen		
Age	Amount	Route
At birth	250 mg	Intramuscular 125 mg in each thigh
2 weeks	»	
4 weeks	»	
6 weeks	»	
8 weeks	»	
3 months	»	
4 months	»	
5 months	»	
6 months	»	

(maximum ALT value of 220 iu/l). Seven of the nine babies with normal enzymes and four of those with abnormal enzymes are positive for e antigen.

None of the biochemistry tests on our carrier babies have been felt sufficiently abnormal to be grounds for carrying out a liver biopsy.

e Antigen

It must be noted that there is a wide variation in proportion of e carriers in various populations. In British blood donors (Barbara *et al.*, 1978), there are three times more male carriers than female, and within the males, 36%

Table 2. — *Maternal transmission of Hepatitis B in different geographical areas.*

Country	Number of infants followed-up	Number of infants HBsAg positive (%)	References
Denmark	17	1 (6.0%)	Skinhoj *et al.* (1976)
Greece	15	1 (6.6%)	Papaevangelou *et al.* (1974)
USA	36	6 (16.6%)	Schweitzer (1975 b)
UK (European)	39	0 —	Derso *et al.* (1978)
UK (Asian)	51	4 (8.0%)	Derso *et al.* (1978)
UK (Negro)	13	4 (31.0%)	Derso *et al.* (1978)
UK (Chinese)	14	9 (64.0%)	Derso *et al.* (1978)
Japan	23	10 (43.0%)	Okada *et al.* (1976)
Taiwan	158	63 (40.0%)	Stevens *et al.* (1975)
Hong Kong	37	26 (70.3%)	Lee *et al.* (1978)

Table 3. — *Mean transaminase levels in infants of chronic HBsAg carrier mothers.*

Mean values	Infants		
	Controls n=26	HBsAg -ve n=97	HBsAg +ve n=15
Age (months)	16.5	9.4	12.5
SGPT (iu/l)	22.4	25.6	64.1
SGOT (iu/l)	46.9	46.2	80.8

n = number tested

carried e as against only 6% of the females. We have observed a very wide ethnic variation in the prevalence of e which correlates very closely with the observed rate of vertical transmission (table 4). However, not all carrier babies are born to e antigen positive mothers, nor do all e antigen positive mothers have carrier babies. Table 5 shows the exact figures for our study. There are three carrier babies, two of them siblings whose mothers are both e and anti e negative, two of the babies are Chinese, the other is Asian. The six negative babies whose mothers are e antigen positive are of interest, as two of them (one Asian and one West Indian) now have anti HBs (i.e. have become acti-

Table 4. — *Ethnic distribution of e antigen carrier state in Hepatitis B carrier mothers.*

Ethnic group	Total tested	e +	%	% vertical transmission
Asian	64	5	8	8
European	43	0	0	0
Afro-Carribean . . .	19	6	32	30
Chinese	19	12	63	64
Total	145	23	16	

Table 5. — *e antigen status of carrier mothers whose babies were followed-up for >3/12.*

	Total tested	e antigen positive	%
Mothers of HBsAg carrier babies	18	15 *	83
Mothers of negative babies	105	6 **	5.7

* 2 remaining mothers also Anti e negative by RIA
1 Chinese mother with 2 carrier babies
1 Asian mother

** 1 West Indian mother with 1 negative + 1 carrier baby
2 Chinese + 1 Asian mother with negative babies
1 Asian + 1 West Indian mother whose babies have Anti HBs.

Table 6. — *e antigen and maternal transmission of Hepatitis B virus.*

Mothers of positive babies e antigen positive	Mothers of negative babies e antigen positive	Reference
15/18 (83%)	6/105 (5.7%)	
17/30 (57%)	3/32 (9.4%)	Beasley *et al.* (1977)
1/1 (100%)	0/16 (0 %)	Skinhoj *et al.* (1976)
10/12 (83%)	0/11 (0 %)	Okada *et al.* (1976)
4/5 (80%)	0/3 (0 %)	Tong *et al.* (1979)

vely immune). Another e antigen positive mother, a West Indian, had one carrier and one negative baby, the others were two Chinese and one Asian.

The correlation of these results with other studies is shown in table 6. Our results agree with several others in that there is about an 80% chance of an e antigen positive mother having a carrier baby. However, our study has shown over a larger number of babies that there are e antigen positive mothers (about 6%) whose babies do not become carriers.

Production of anti HBs

Despite considerable exposure at birth, very few babies have been observed to respond immunologically to their mother's antigen. Of 248 sera from 142 babies tested by RIA (Ausab, Abbott Laboratories), only four babies have been found to have become actively immune (table 7). One of these babies (case 1) was observed to have a subclinical hepatitis at three months with HBs antigenaemia, subsequently becoming HBsAg negative and anti HBs positive. The other two Asian babies, who are siblings, may also have had a

Table 7. — *Anti HBs studies in babies born to HBsAg carrier mothers.*

Total number of babies tested 142
Number Anti-HBs positive 4 (2.8%)

Ethnic group	Age when first Anti-HBs positive	Comments
1. Asian	8 months	Sub clinical acute hepatitis at three months Mother e Ag positive
2. Negro	3 months	Mother e Ag positive
3. Asian	21 months	Not tested since birth Mother e negative
4. Asian	6 months	Not tested since birth Sibling of Case 3

subclinical HBs antigenaemia, but the times of follow-up did not permit the observation of this. The fourth baby, a West Indian, was anti HBs positive from the age of three months. It is interesting that two of the three mothers whose babies have produced anti HBs are e antigen positive.

Mechanisms of infection

There are three stages at which transmission can occur; in utero, at delivery, and in the post-natal period. True in-utero infection in hepatitis B is fairly rare, as the foetus is not infected if the mother has hepatitis during her pregnancy, but is HBsAg negative at the time of delivery. We also observe in infants that the time of development of the carrier state is consistent with infection at the time of birth. However, there is on record one case where a true in-utero infection had taken place (Schweitzer, 1975b). A mother who had acute hepatitis at six months gestation, but was negative at the time of delivery, gave birth to a child who was HBsAg positive and has remained so since. The HBsAg in the cord blood could not have come from the mother, but must have been the result of an infection established in the child before birth.

Infection during delivery in both carrier mothers and mothers with acute hepatitis is the most likely time of infection. Possible routes include materno-fetal transfusion, the contamination of any birth injury or the ingestion of maternal blood or other body fluids. There is evidence that maternal amniotic fluid and gastric fluid aspirated from babies during resuscitation contain HBsAg (Lee *et al.*, 1978). The presence of HBsAg in the cord blood is not a reliable indicator of infection; in our study, only ten out of sixty two infants whose cord bloods contained HBsAg became carriers, and two babies whose cord bloods are HBsAg negative became carriers within the same time scale.

It is difficult to assess infection in the neonatal period when there is such a massive exposure at birth. However, although HBsAg can be demonstrated in breast milk, there is no evidence to suggest that it has been harmful to any baby (Boxall *et al.*, 1980).

PREVENTION AND CONTROL

Immunoglobulin

There are three ways in which immunoglobulin could be used:

1) Some cases of acute hepatitis B late in pregnancy could be prevented by offering immunoglobulin to pregnant contacts, especially sexual contacts, of acute cases of hepatitis B.

Table 8. — *Immunoglobulin administration to babies born to HBsAg carrier mothers.*

Treated			Untreated			Reference
Total	HBsAg+	Anti HBs+	Total	HBsAg+	Anti HBs+	
2	0	1	2	1	0	Kohler *et al.* (1974)
34 [a]	19	6	39	25	1	Beasley *et al.* (1978)
21 [b]	0	4	20	5	1	Reesink *et al.* (1979)
3 [c]	2	0				
1 [b]	1	0				Boxall *et al.* (1980)
42 [d]	21	11	35	32	1	Beasley *et al.* (1981)
40 [e]	9	19				

[a] Single dose at or close to birth.
Onset of HBs antigenaemia at an earlier age in control group.

[b] Repeated high doses of anti HBs monthly for six months from birth.

[c] As b, but first injection four to five days after birth.

[d] Single dose at birth.

[e] Doses at birth, three and six months.

2) It should be given to babies whose mothers have acute hepatitis B late in pregnancy. Repeated small doses are advised until the mother has recovered clinically and virologically. Unfortunately, the baby born to the mother who develops acute hepatitis after delivery may not be protected by immunoglobulin. Immunoglobulin therapy in cases of maternal hepatitis is possible because of the limited period of risk as the mother will eventually recover and be HBsAg negative.

3) Immunoglobulin administration to the babies of carrier mothers carries the problem of continued exposure to the mother's and any sibling's virus for the rest of the life of the child. Table 8 shows the results of studies into the use of hyperimmune globulin for such babies. These results show that in some cases, the development of the carrier state can be prevented by the administration of hyperimmune globulin, but that the therapy must be started immediately after birth, and that a single dose is unlikely to be effective. However, the most comprehensive study (Beasley *et al.*, 1981) in a very high risk group, has shown that there are some babies in whom even a three dose scheme started immediately after birth has not prevented the establishment of the carrier state. We have studied a Chinese baby to whom we gave repeated doses of immunoglobulin as in table 1. Although he remained free of HBsAg for five months, long term follow-up showed that he acquired the carrier state outside this period. It is possible that in some populations the

natural response to Hepatitis B virus is the development of the carrier state, whenever and however that exposure occurs.

In the long term, for the protection of the babies and towards the gradual reduction in the prevalence of the carrier state, we must help these babies to become actively immune to their mother's virus. As so few of them produce anti HBs naturally, we must consider the use of a hepatitis B vaccine. As the carrier state develops within the first few months of life, vaccine would have to be given very early, possibly with a covering injection of specific immunoglobulin. If this is effective, it should be given to all babies of carrier mothers irrespective of their e antigen status.

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