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A prospective study of 18 infants of chronic HBsAg mothers

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SUMMARY 28 of 1002 pregnant Sicilian women (2·8%) were asymptomatic HBsAg chronic carriers. 18 children of these women were followed and at least 15 of them showed evidence of transplacental infection with HBsAg, resulting either from the presence of the antigen in cord blood, or from the development of the corresponding antibody in the serum within the first 2 months of life. Despite this, only 2 or 3 of the infants developed chronic antigenaemia from age 2–4 months. Only the infants whose mothers were HBeAb-negative, and who themselves remained HBsAb-negative during the first months of life, became HBsAg carriers. On the basis of these results, a strategy is suggested for selecting infants from areas with a high prevalence of HBsAg carriers so that they can be given passive immunisation with hyperimmune globulin.

The application of new techniques for demonstrating hepatitis B surface antigen (HBsAg) to the study of maternofetal transmission of hepatitis B (so-called vertical transmission) has raised more questions than it has resolved. Unresolved problems include the prevalence of cord blood antigenaemia in children of chronic carrier mothers, the successive development, duration, and clinical implications of the antigenaemia in these children, and the possibility of its prevention.

In order to obtain information on these topics, we identified a group of pregnant women who were asymptomatic chronic HBsAg carriers, and followed their children for several months after birth, with clinical and laboratory examinations.

Our study indicated that HBsAg-positive mothers usually transmit the antigen to their babies, but also that only a few of these infants develop persistent antigenaemia with or without signs of hepatitis. On the basis of these findings we suggest a possible strategy for the prevention of persistent HBs antigenaemia in children of carrier mothers.

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Materials and methods

1002 unselected pregnant women admitted to this maternity hospital, where over 6000 deliveries a year take place, were screened for HBsAg by the reverse haemagglutination method (Hepanosticon, Organon). All the positive sera were retested by radioimmunoassay (AUSRIA II, Abbott Laboratories) and confirmed to be positive, and determinations of bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT) were made. A second radioimmunoassay for HBsAg was made after 3–6 months in order to confirm the chronic carrier state.

The HBsAg-positive women were also tested for HBcAb, by radioimmunoassay (CORAB, Abbott Laboratories), and for HBeAg and HBeAb by immunodiffusion techniques, using e antigen and antibody kindly supplied by Dr Linsen (Copenhagen).

The babies of the HBsAg-positive mothers were examined clinically at monthly intervals, and their sera tested for HBsAg (AUSRIA II, Abbott Laboratories), HBsAb (AUSAB, Abbott Laboratories), bilirubin, AST, and ALT. The babies were all formula fed. When available, their fathers were also studied.

Results

28 of the 1002 women (2·8%) were asymptomatic

chronic carriers of HBsAg. None had a history of clinical hepatitis, jaundice, or liver enlargement; serum transaminases and bilirubin levels were normal. The 28 women were informed of their condition and advised that their babies should be periodically examined. Eventually, 18 of the 28 children of chronic carrier mothers were kept under observation for 3–14 months. The results were as follows (Figure). (1) Five of the 9 cord bloods examined were HBsAg-positive. One child with HBsAg-positive cord blood was born by caesarean section (Case 4). But the positivity for HBsAg in the cord blood was transient as all the sera examined 2–3 days later were consistently HBsAg-negative. (2) In 10 (56%) of the 18 children a weak but definite positivity for HBsAb was found for the first time in the sera obtained at 1–2 months of age. None of these children had previously been HBsAg-positive, apart from 3 transient positives in cord blood (Cases 4, 9, and 14, Figure). Even the HBsAb-positivity was generally transient; only in Case 9 was it still present in the last examination at 7 months. (3) Four of the 18 children became HBsAg-positive between 2 and 4½ months. This incubation period is in agreement with previous work, suggesting that infection with HBsAg usually takes place during the immediate perinatal period. Details of these 4 cases were as follows.

Case 1. This asymptomatic infant, whose cord blood was HBsAg-positive, showed HBsAg positivity with slightly increased AST and ALT only on one other occasion at 4½ months. This positivity was transient and was followed by appearance of HBsAb at age 10 months.

Case 3. HBsAg was found for the first time at 4 months, accompanied by markedly increased AST and ALT and by slight liver enlargement without jaundice or other clinical symptoms. The raised transaminase levels persisted during the observation period (up to 14 months). A liver biopsy at 7 months showed histological features of chronic hepatitis (interstitial fibrosis with mononuclear infiltrates, with some disorganisation of the lobular architecture).

Case 11. At 2 and at 3 months this asymptomatic child, who had been previously HBsAg-negative, showed HBsAg positivity and moderately increased transaminase levels.

Case 18. HBsAg was present from age 2 months up to the last examination at 6 months. Serum transaminases were normal, and there were no clinical symptoms.

A negative correlation was found between early

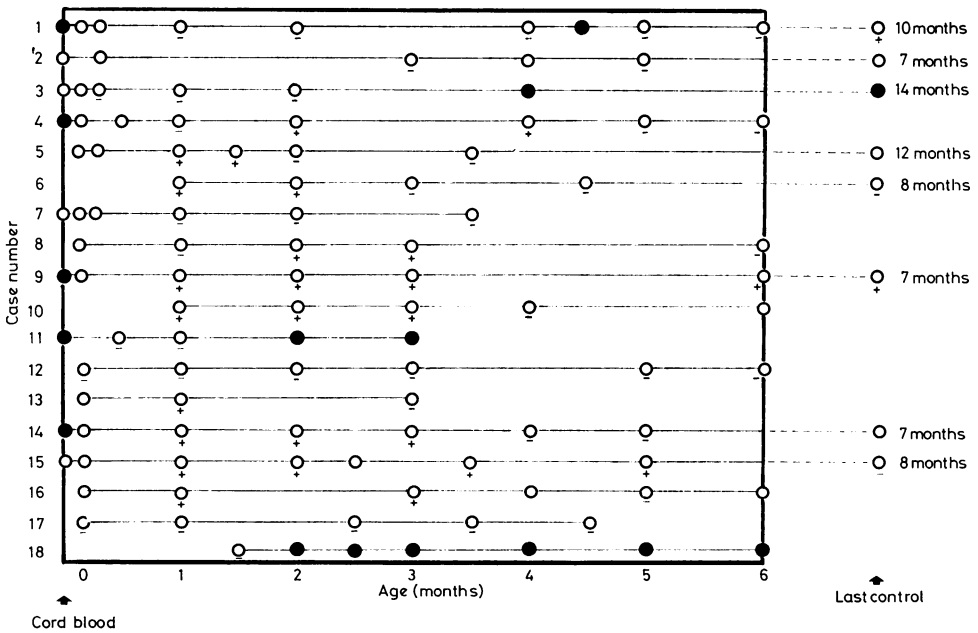

Figure *HBs antigen and the corresponding antibody in 18 children of chronic HBsAg carrier mothers.* + = *positivity*, − = *negativity for HBsAb* ● = *positivity*, o = *negativity for HBsAg.*

Table 1 *Hepatitis-associated antigens and antibodies in 18 infants of HBsAg carrier mothers and in their parents*

Case	*Father*		*Mother*				*Cord serum*	*Infant*	
	HBsAg	*HBsAb*	*HBsAg*	*HBcAb*	*HBeAg*	*HBeAb*	*HBsAg*	*HBsAb*	*HBsAg*
1	−	−	+	+	−	+	+	−	+
2	−	−	+	+	−	+	−	−	−
3	−	−	+	+	−	−	−	−	+
4	ND	ND	+	+	ND	ND	+	+	−
5	−	+	+	+	−	−	ND	+	−
6	−	+	+	+	−	−	ND	+	−
7	−	±	+	+	−	+	−	−	−
8	−	+	+	+	−	+	ND	+	−
9	−	−	+	+	−	+	+	+	−
10	−	+	+	+	−	+	ND	+	−
11	−	−	+	+	−	−	+	−	+
12	−	±	+	+	−	+	ND	−	−
13	−	−	+	+	−	+	ND	+	−
14	+	−	+	+	−	+	+	+	−
15	−	+	+	+	−	+	−	+	−
16	−	−	+	+	−	+	ND	+	−
17	−	+	+	+	−	−	ND	−	−
18	−	+	+	+	ND	ND	ND	−	+

+ = Positive, − = negative, ND = not done.

positivity for HBsAb and the development of HBsAg positivity: all 10 HBsAb-positive children remained HBsAg-negative, while 4 of the 8 HBsAb-negative children became HBsAg-positive. This difference is significant at the 0·01 level by the χ^2 method.

(4) 16 of the 18 mothers were studied for HBeAg and HBeAb (Table 1). All were HBeAg-negative, while 11 were HBeAb-positive. Persistent HBsAg positivity developed, at 3 and 4 months of age, in 2 of the 5 children born to HBeAb-negative mothers, and in none of the 11 children born to HBeAb-positive mothers. Only one of these developed HBsAg positivity at age 4½ months; this rapidly disappeared and was followed by the development of HBsAb (Case 1, Figure).

This difference is significant at the 0·025 level.

(5) All the 18 HBsAg-positive mothers, including those whose children became HBsAg positive, were tested for HBcAb and found positive.

(6) Only one of the 17 fathers studied was a HBsAg carrier like his wife. The child born to this couple was positive for HBsAb at 2 and 4 months, and at 6 months he was still HBsAg-negative.

Discussion

While there may well be pronounced ethnic differences in the frequency with which HBsAg is transmitted by carrier mothers to their babies, recent studies using sensitive detection methods have shown this frequency to be quite high in all countries (Table 2).

Table 2 *Newborn infants of chronic carrier mothers who were followed up*

Country	*Authors*	*Year*	*Carrier mothers (%)*	*Infants*			*Method**	*Follow-up (months)*
				Studied	*Positive*	*Persistently positive*		
Denmark	Skinhøj *et al.*	1972	0·12	36	0	0	GEP	3–12
		1976		30	1	1	RIA	48–60
Pakistan	Aziz *et al.*	1973	1·52	18	1	1	CEP	>70
USA	Schweitzer *et al.*	1973	0·49	21	1	1	CEP	≥3
	Gerety and Schweitzer	1977		14	6	5	RIA	>6
Thailand	Punyagupta *et al.*	1973	9·39	14	0	0	ID	6
Greece	Papaevangelou *et al.*	1974	3·27	15	1	1	RIA	6
Taiwan	Anderson *et al.*	1975	7·50	43	27	≥20	CF-RIA	1–18
	Stevens *et al.*	1975	15·20	158	63	35/38	RIA	1–18
Japan	Okada *et al.*	1975	2·32	11	8	8	IAHA	8–26
		1976	2·50	23		12	IAHA	≥12
Italy	Chircu *et al.*	1975	2·25	6	1	0	RIA	2–5
France	Dupuy *et al.*	1978	0·63	12	8	1	RIA	6–18
Italy	Present series		2·80	18	4	2 or 3	RIA	3–14

*GEP = Gel electrophoresis, RIA = radioimmunoassay, CEP = counter electrophoresis, ID = immunodiffusion, CF = complement fixation, IAHA = immunoadherence haemagglutination.

Direct evidence of maternofetal transmission is given by the HBsAg positivity of cord blood at birth. In this respect, in agreement with other recent studies (Schweitzer *et al.*, 1973; Boxall and Davies, 1974; Papaevangelou *et al.*, 1974; Chircu *et al.*, 1975), we found a high percentage of positivity (5 of the 9 cord bloods examined). But the present study gives additional, indirect evidence of maternofetal transmission of HBsAg even in those children in whom HBsAg has not been directly demonstrated. In fact, many infants of our series, previously repeatedly HBsAg-negative by radioimmunoassay, developed antibodies against this antigen within the first 2 months of life. A postnatal infection of these infants is extremely unlikely, because of this high frequency of an early appearance of HBsAb. By adding to the subjects with HBsAg-positive cord blood those who developed HBsAb early in life, we have direct or indirect evidence of fetal infection with HBsAg in 13 of the 18 infants. We could add to these another 2 infants (Cases 3 and 18, Figure) in whom HBsAg appeared at 4½ and at 2 months, even if postnatal infection cannot be ruled out for these subjects, particularly for Case 3.

Despite this high transmission rate, only a few children (2 or 3 out of 18 in our series) developed persistent HBs antigenaemia. It is probable therefore that in most subjects there are some protective factors.

Okada *et al.* (1976), in a series of mother-child pairs recently studied in Japan, found that the children of HBeAg-positive mothers all became HBsAg-positive, while the children of mothers with HBeAb remained HBsAg-negative. More recent studies (Gerety and Schweitzer, 1977; Dupuy *et al.*, 1978) have raised some doubts about the infecting role of maternal HBeAg, while the protective role of maternal HBeAb has been fully confirmed: in these series, HBs-antigenaemia developed in only one child of a HBeAb-positive mother, but was transient and was rapidly followed by the appearance of HBsAb. Our series comprises one other child with an identical pattern, and clearly confirms that maternal HBeAb always prevents the development of chronic HBs antigenaemia in these children. As (as in the study of Papaevangelou *et al.*, 1974) all the 18 mothers of our study were HBcAb positive, the results do not suggest that maternal HBcAb prevents HBsAg infection of the conceptuses.

By contrast, a significant protective role is played by the HBsAb produced by the infant from the first weeks of life. The 3 infants who became persistently HBsAg-positive were all born to HBeAb-negative mothers, and none of them had been HBsAb-positive in the first 2 months of life. On the other hand, none of the children whose mothers were HBeAb-positive, or who themselves had been HBsAb-positive, became a HBsAg carrier.

On the basis of these results, a strategy is indicated to prevent persistent antigenaemia in children of HBsAg carrier mothers in areas with a high prevalence of HBsAg carriers. (1) Each pregnant woman should be tested for HBsAg. (2) Each HBsAg-positive woman should be tested for HBeAb. (3) Each child of an HBsAg+, HBeAb− mother is at risk and administration of HBsAg hyperimmune gammaglobulin should be considered, or (4) each child of an HBsAg+, HBeAb− mother who remains HBsAb− during the first 6 weeks of life is at risk and administration of HBsAg hyperimmune gammaglobulin should be considered.

Kohler *et al.* (1974) and Dosik and Jhaveri (1978) have suggested that a chronic HBsAg carrier state might be prevented by the administration of hyperimmune HBsAg globulins in the immediate postnatal period. A control trial of such treatment in infants selected in the above fashion could provide useful data.

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