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Acquisition of hepatitis B antigen in the newborn period

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Summary

This paper describes six mother and infant pairs where the mother developed serum hepatitis during pregnancy. These findings are compared with those in three Australian antigen carrier mothers and their babies. The literature is also reviewed and it is concluded that neonatal hepatitis seldom occurs in infants whose mothers have hepatitis early in pregnancy or are chronic carriers of Australia antigen. In contrast the risk of infection of infants born to mothers who develop serum hepatitis later in pregnancy or in the puerperium approaches 50%.

SINCE Stokes *et al.* (1954), transmitted serum hepatitis to volunteers by injecting sera from a carrier mother and her infant with neonatal hepatitis, it has been assumed that this infection can cross the placenta to cause congenital liver disease. The availability of tests for Australia antigen, which is a good marker of the viraemic phase of serum hepatitis, now makes it possible to estimate the importance of this cause of neonatal hepatitis. This paper presents the findings in patients followed at the Virus Reference Laboratory, and reviews the results of similar studies in other countries.

Countercurrent electrophoresis was used for routine screening tests, and complement fixation tests and electronmicroscopy were used as needed. Radioimmunoassay was performed with 'Ausria' kits (Abbott).

Hepatitis in pregnancy is rather uncommon. In 1968 Sever and White estimated its frequency as about 1/10,000 pregnancies in the United States. In London during 1969 and 1970 only nineteen cases were tested at the Virus Reference Laboratory and of these five were Australia antigen positive. In the first half of 1973 six mothers were tested because of 'hepatitis' in the last trimester of pregnancy. None were positive and all the cord bloods were negative. The babies were all healthy. In the same period four asymptomatic mothers were tested because their infants had neonatal hepatitis. The sera from all four mothers and infants were Australia antigen negative even by radioimmunoassay. One of these mothers had another affected child.

TABLE 1. Au+ hepatitis in pregnancy

No. 1	Mother	Au+ hepatitis at delivery; Au- 1 week later
	Father	Au- but tattoo about 6 months previously
	Baby	Cord blood Au - (including RIA) 10 days Au+ 3 years; still Au+ Liver—hepatitis and SH particles on biopsy Normal sibling born subsequently
No. 2	Mother	Au+ hepatitis, onset 10 days post partum
	Father	'Hippie hepatitis' 3 months previously Not tested
	Baby	Au+ 3 weeks (first test) 2½ years—still positive 'Biochemical' liver disease
No. 3	Mother	Au+ hepatitis at delivery (Overland travel from Australia)
	Father	Well—not tested
	Baby	Cord blood Au - (including RIA) 3 months—Au -
No. 4	Mother	Au+ hepatitis onset 36 weeks Negative at delivery
	Father	Not tested
	Baby	Cord blood Au - (including RIA) 3 months—Au -
No. 5	Mother	Au+ hepatitis, onset 14 weeks (? drug abuse) Negative at delivery
	Father	Not tested
	Baby	Cord blood Au - (including RIA) Lost to follow up
No. 6	Mother	Au+ hepatitis at delivery Drug abuse and injection in Middle East
	Father	Not tested
	Baby	Cord blood negative—Au+ at 12 weeks Lost to follow up

Since 1969 only six mothers with Australia antigen positive hepatitis have been followed, and the salient features of each case are given in Table 1. The infant of the mother who had hepatitis early in pregnancy escaped infection (Case 5). The two infants (Cases 3 and 4) who escaped infection, even though the onset of their mothers' hepatitis was near delivery, were the only two in the series who were separated from their mothers after birth. The other three babies (Cases 1, 2 and 6) became antigen positive during the first weeks of life and have remained long term

carriers. Although their liver function tests have become abnormal the children have remained clinically well. A biopsy was performed in Case 1 and showed histological hepatitis. The liver cell nuclei contained SH 'virus' particles when examined electronmicroscopically. None of the samples of cord blood contained Australia antigen even when tested by radioimmunoassay, and concentrates of colostrum from Cases 1 and 2 were negative by electronmicroscopy. An incidental point is that most of these mothers fell into the 'hippie hepatitis' group and that two had probably acquired the infection from their husbands.

Table 2 shows the findings in three instances of pregnancy in Australia antigen carriers. The mothers were all tested at their first antenatal visit. By term, two had become antigen negative by electrophoresis, but one of these was again strongly antigen positive 3 months later. None of the babies was affected.

Table 3 gives the findings in an infant who received one unit of Australia antigen positive blood amongst 10 units exchange transfused on the first day of life. Antigen positive hepatitis developed 6 weeks later and at 4 months of age the baby was still antigen positive, although clinically well.

These findings accord well with those from other centres. Australia antigen was not detected in cord bloods from infants of eighty carrier mothers from centres in Denmark, U.S.A., India and Pakistan (Skinhøj *et al.*, 1972; Smithwick and Go, 1970; Aziz *et al.*, 1973; Kukowski *et al.*, 1974). There is little information about the situation when the mother has antigen positive hepatitis, but most accounts (e.g. Turner *et al.*, 1971) of affected infants report negative results on the cord blood. Some instances of positive cord blood have been reported,

TABLE 2. Au carriers in pregnancy

Pair 1	Mother	Au+ carrier (detected first trimester) Au− at delivery Au+ 3 months later
	Baby	Cord blood and 3 month serum Au−
Pair 2	Mother	Au+ carrier (detected first trimester) Au+ at delivery
	Baby	Cord blood and 3 month serum Au−
Pair 3	Mother	Au+ carrier (detected first trimester) Au− at delivery
	Baby	Cord blood negative, lost to follow up

TABLE 3. Transfusion of Au+ blood

Mother	Well
Baby	Exchange transfusions at birth 1/10 Units Au+ Next day baby's serum Au+ (RIA only) 6 weeks Au+ hepatitis 4 months still Au+

TABLE 4. Source of Infection

Timing of mother's hepatitis	Number of affected babies
Au+ at delivery	
acute hepatitis	12
carrier	4
Au+ hepatitis ante partum	
< 2 months	3
> 2 months	3
Au+ hepatitis post partum	
< 2 months	4
2–6 months	0
Baby transfused in first week	1
Mother transfused within 2 months delivery	1

Merrill *et al.* (1972); Schweitzer *et al.* (1972); Gillespie *et al.* (1970); Turner *et al.* (1971); Cossart *et al.* (1972); Wright *et al.* (1970); Keys *et al.* (1972); Papaevangelou (1973).

but in at least one of these (positive by radioimmunoassay only) the baby escaped infection (Schweitzer *et al.*, 1972).

Table 4 has been compiled to show the source of infection in the twenty-eight babies with Australia antigen positive hepatitis so far reported. More than 80% were born to mothers who had acute antigen positive hepatitis late in pregnancy or in the puerperium, and for more than half the onset of illness coincided with delivery and had presumably induced labour. It was not possible to assess the incubation periods from the information given but in all the cases where serial testing of the infant was possible antigenaemia developed between the second and twelfth weeks of life. The two infants whose hepatitis resulted from transfusion were also antigen positive by this age. The onset of abnormalities in liver function tests followed after variable intervals, but in almost all cases antigenaemia persisted indefinitely. This is probably because of the limited immune competence of infants. The outlook for these babies is uncertain and one at least has progressed to cirrhosis (Wright, Perkins and Bouch, 1970) while another has recovered and become antigen negative (Keys *et al.*, 1972).

Although hepatitis in pregnancy is rare, the Australia antigen carrier state is common, but seems to be of little importance for the infant. Table 5 gives the results of studies in four countries and shows that as regards foetal loss, and liver disease in infants the carriers seem unaffected. However, two of the sixty-one infants did become antigen positive, both in Greece. It may be speculated that this geographical difference is related to the predominance of the a+y+ subtype in Greece and the a+d+ subtype in Denmark. Much longer term studies will be needed, however, to determine that infants born to carriers do not have latent infection which can be activated later in life.

TABLE 5. Au+ in first half of pregnancy (prospective studies)

	Acute hepatitis	Carrier
Foetal loss	?	3/82 i.e. No increase (Denmark, Skinhøj *et al.*, 1972)
Congenital abnormalities	0/6 (U.S.A. Schweitzer *et al.*, 1972)	0/68 (Denmark, Skinhøj *et al.*, 1972)
Liver disease in infants	2/6 (U.S.A. Schweitzer *et al.*, 1972)	4/68 Transient jaundice but Au – (Denmark, Skinhøj *et al.*, 1972)
		0/14 (Pakistan, Aziz *et al.*, 1973)
Infant Au+ by 6 months age	2/6 (U.S.A. Schweitzer *et al.* 1972)	0/36 (Denmark, Skinhøj *et al.*, 1972)
	1/2 (Pakistan, Aziz *et al.*, 1973)	0/14 (Pakistan, Aziz *et al.*, 1973)
		2/11 (Greece, Papaevangelou, 1973)

It is not clear why there should be such a great difference in infectivity for the foetus between hepatitis and antigen carriage in pregnancy. From the circumstantial evidence of the antigen negative cord bloods it seems that infection is acquired during delivery rather than in utero. There is undoubtedly a great likelihood that the baby will swallow some blood stained liquor during even the last traumatic delivery, and in any case there is probably sufficient maternal blood leaked across the placenta during delivery to constitute exposure. However, the blood of hepatitis patients and carriers seems about equally infectious when injected into adults, so perhaps the placenta permits the passage of protective antibody (? anti-core) from the carriers to their offspring.

It is impossible to prevent exposure of infants to their mothers' blood but as congenital infection seems seldom to be manifest at delivery it might be possible to prevent infection by injecting the newborn infants with specific immunoglobulin made from the plasma of healthy blood donors in whom anti-Australia antibody has been detected. On the evidence so far available it would seem that infants of mothers with active hepatitis have about a 50% risk of becoming infected, so that the assessment of immunoglobulin prophylaxis in this group is urgently needed. In view of the low reported incidence in infants born to carrier mothers it is doubtful if routine testing of antenatal patients can be justified. Some support for this view also comes from the low incidence of positive Australia antigen tests in infants with jaundice. Between January and June this year twenty-one babies jaundiced between the second and fourth weeks of life and three jaundiced between the second and sixth month have been tested at the Virus Reference Laboratory, and all were negative.

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Discussion

In answer to comments by Professor Wright (Southampton) and Professor Aagenaes of Oslo who suggested the possibility of intra partum exposure to hepatitis B antigen from episiotomy wounds and transplacental transfusion, Dr Cossart agreed that such factors may account for the varying incidence of hepatitis B antigen in the cord blood but felt that the use of tests of varying sensitivity was also an

important factor. If infection does occur at the time of delivery, it is difficult to explain the short incubation period of 3 to 4 weeks which is exceptional in experimental situations.

Dr Reuben Dubois, Denver, reported on experience in the use of gammaglobulin in the prevention of transfer of the antigen from the mother to infant. The infants of seven mothers who had acute hepatitis with antigenaemia at the time of delivery were studied. Four received no therapy. Antigenaemia appeared at 6–8 weeks of age and persists. The infants are asymptomatic but have elevated transaminases. Two infants were given 0·1 cc/lb of high titre antibody (>1/200,000) to hepatitis B antigen. These infants have not developed antigenaemia at 6 and 12 months of age. One infant received commercial gammaglobulin with an antibody titre of 1 in 64, but by 6 weeks had developed antigenaemia with mild elevation of serum transaminases.

High titre antibody to hepatitis B antigen was also given to the infant of an asymptomatic carrier because her three other children were hepatitis B antigen positive and had raised serum transaminases. At 6 months of age this infant remains free from antigen. Clearly, further follow-up of these cases and controlled trials will be necessary.