The outcome of hepatitis B virus infection in pregnancy

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Summary

The literature concerning hepatitis B in pregnancy is reviewed and problems of management of both the acute and chronic infections are discussed.

CLINICAL hepatitis occurs only about once in 20 000 pregnancies in Western Europe and North America (Sever and White, 1968) but it seems to be much more common in pregnant women in areas such as the Middle East (Zondek and Bromberg, 1947) and Africa where hepatitis is hyperendemic in the general population. In both high- and low-incidence areas the frequency and severity of the illness increase greatly during the last trimester (Table 1) and in many countries hepatitis is a significant cause of maternal mortality. As premature labour often accompanies the onset of jaundice the perinatal mortality is also high (Table 2).

TABLE 1. Hepatitis at different states of pregnancy

Country	No. of cases (% mortality)		
	1st trimester	2nd trimester	3rd trimester
Iran (Borhanmanesh <i>et al.</i> , 1973)	6 (16)	17 (17)	59 (33)
India (Malkani and Grewel, 1957)	8 (38)	55 (20)	81 (59)
USA (Siegel <i>et al.</i> , 1966)	4 (0)	7 (14)	22 (0)
Israel (Zondek and Bromberg, 1947)		6 (0)	15 (34)
Denmark (Hammerli, 1966)		3 (0)	85 (1)
Australia (Bennett <i>et al.</i> , 1967)		19 (0)	109 (0)

On the other hand, a prospective study of viral infection in pregnancy (Siegel, Fuerst and Peress, 1966) has shown that there is no increase in fetal loss or congenital abnormality following hepatitis in the first half of pregnancy. The suggestion (Stoller and Collmann, 1965) that maternal hepatitis occurring near the time of conception is associated with an increased incidence of Down's syndrome has not

TABLE 2. Perinatal mortality of infants born to mothers with acute hepatitis

Country	No. of babies	Percent mortality
India (Malkani and Grewel, 1957)	34 (full term)	18
	78 (premature)	52
Israel (Zondek and Bromberg, 1947)	22 (full term)	0
	5 (premature)	80
Iran (Borhanmanesh <i>et al.</i> , 1973)	32 (mother's illness mild)	22
	29 (mother's illness severe)	66
Ghana (Mansell, 1955)	15 (all cases)	60
U.S.A. (Siegel <i>et al.</i> , 1966)	65 (all cases)	8
U.S.A. (Adams and Combs, 1965)	28 (all cases)	14

been substantiated by later studies (Dietzman *et al.* 1972).

Ever since Stokes *et al.* (1954) described a family where two children developed neonatal hepatitis and showed that their mother was a persistent carrier, it has been widely believed that hepatitis B may be an important cause of 'congenital' liver disease. With the advent of hepatitis B surface antigen (HB_sAg) tests it has become possible to assess the situation further. In England about 20% of pregnant patients with hepatitis are HB_sAg-positive (Cossart and Cohen, 1976); this is a similar proportion to that found amongst other young adults with hepatitis. In the Middle East, however, Christie *et al.* (1976) have reported that very few pregnant hepatitis patients are HB_sAg positive. It is likely that there are great differences between countries in this respect.

The infants born after pregnancies complicated by jaundice seldom suffer from clinically obvious liver disease (Hsia, Taylor and Gellis, 1952; Adams and Combs, 1965) but when the offspring of the mother who had hepatitis B are tested, many are HB_sAg positive and some have biochemical and histological evidence of liver disease (Gillespie *et al.*, 1970; Wright *et al.*, 1970; Turner *et al.*, 1971; Marshall and Dudgeon, 1972).

The proportion of infected infants is low when the cases of maternal hepatitis occur during the first half of pregnancy, but it rises to about 50% when the onset is within 4 weeks before or after delivery (Table 3).

TABLE 3. Risk of infection in infants whose mothers develop acute hepatitis within 4 weeks before or after delivery

Reference	Country	No. of infants	No. cord blood HBsAg+	No. follow-up HBsAg+
Holzbach (1972)	U.S.A.	2	0	0
Schweitzer <i>et al.</i> (1973)	U.S.A.	19	2	13
Merrill <i>et al.</i> (1972)	U.S.A.	5	1	4
Cossart and Cohen (1976)	England	6	0	3

The situation regarding hepatitis B carrier mothers is much less clear (Schweitzer *et al.*, 1973). It can be seen from Table 4 that carriers in Denmark and Greece seldom transmit to their infants while those in Taiwan often do. The reason for this difference and the mechanism of transmission are poorly understood.

TABLE 4. Risk of infections in infants whose mothers are hepatitis B-carriers

Reference	Country	No. of infants	No. cord blood HBsAg+	No. follow-up HBsAg+
Skinhøj <i>et al.</i> (1972)	Denmark	53	0	0
Aziz <i>et al.</i> (1973)	Pakistan	17	0	0
Papaevangelou, Hoofnagle and Kremastinou (1974)	Greece	14	2	0
Schweitzer <i>et al.</i> (1973)	U.S.A.	21	0	0
Stevens <i>et al.</i> (1975)	Taiwan	103	21	63

Many infants born to HBsAg-positive mothers do not have detectable antigen in their cord blood (Smithwick and Go, 1970; Skinhøj *et al.*, 1972), but some of these HBsAg-negative infants subsequently develop antigenaemia (Table 3). Conversely infants with HBsAg-positive cord blood may rapidly become negative. Although they have clearly been exposed, some of these infants produce no subsequent evidence of infection.

The age at which infected infants become HBsAg-positive varies, but it is usually before the sixth week of life (Merrill, Dubois and Kohler, 1972; Schweitzer *et al.*, 1973; Hitchins, Gostling and O'Driscoll,

1974). This suggests that transmission occurs during the last few weeks of gestation if an average incubation period of 90 days is expected. However, the chance of avoiding contact with maternal blood during delivery is so remote that it is possible that all infants are exposed at that time and that some failure of the mother's infection governs the outcome in the infant.

The titre of the maternal antigen correlated well with the likelihood of transmission in Taiwan (Stevens *et al.*, 1975) but not in England (Cossart and Cohen, 1976). In any event the correlation could well be indirect since the titres found in acute hepatitis patients are usually higher than those in asymptomatic carriers.

The subtype of the antigen is also unlikely to explain the difference between individuals since the prevailing subtype is *ad* amongst the 'non-transmitting' carriers in Denmark and England but *ay* in Greece, while the 'transmitting' carriers in the Far East have the *ad* subtype. Not enough is known about the minor determinants in this context, but they may reflect important strain differences amongst hepatitis B viruses.

So far, the most important factor recognizable in determining transmission from mother to infant is the activity of the mother's liver disease, but this is difficult to assess during pregnancy because of the physiological alterations in liver function. Many 'healthy' carriers have chronic hepatitis which is only revealed by specific investigation and in at least one larger series from the U.S.A. (Schweitzer, Edwards and Brezina, 1975) where 'carriers' were reported to have transmitted hepatitis to their infants it is clear that the authors' definition included mothers with chronic hepatitis following an acute attack of 'hippie hepatitis'. It is still too early to know whether the *e* antigen will be a reliable indicator of the risk of transmission and in particular serve to identify those exceptional carriers who are at risk of producing severely affected infants in subsequent pregnancies (Kohler *et al.*, 1974).

Very little is known about the outlook for infants who acquire hepatitis B in the first few months of life. The first reports showed that severe (Wright *et al.*, 1970; Marshall and Dudgeon 1972; McCarthy, 1973) and even fatal (Fawaz *et al.*, 1975; Kohler *et al.*, 1974) liver disease could occur but as more cases have been studied it has become obvious that long term, asymptomatic carriage is the more usual result. This is to be expected in view of the immaturity of the immune response at this age, but it is not yet known how many of the infants are able to clear the antigen as they get older (Dahlquist and Nordenfelt, 1974).

Those who remain persistent carriers may suffer from chronic liver disease in later life. Familial

TABLE 5. Hepatitis in pregnancy—summary of treatment

HBsAg-Positive	HBsAb-Negative
(1) Acute hepatitis <i>Before 28th week</i> —No action (no risk congenital defect) <i>After 28th week</i> —Conservative treatment (risk premature labour). If mother still HBsAg+ at delivery treat as below. + 4 weeks delivery—50% risk of infecting infant. Test cord blood. If negative, give infant 500 mg specific hepatitis B immunoglobulin immediately and if infant still HBsAg-negative repeat in 6 weeks. Follow-up infant for 1 year. If cord blood HBsAg-positive retest infant in 48 h. If negative or only HBsAg-positive by HA and RIA, give specific immunoglobulin. If strongly positive, follow-up until negative. No need to separate mother and infant or to stop breast feeding if established.	No action (no risk congenital defect). Conservative treatment (risk premature labour). ? Little risk clinical illness in infant. No need to separate mother and infant or to stop breast feeding if mother well enough. No contraindication to giving infant 250 mg normal immunoglobulin but probably unnecessary.
(2) Contact hepatitis <i>Inoculation injury</i> —Treat as if not pregnant. <i>Household contact</i> —No action unless contact husband has acute hepatitis when give specific immunoglobulin (500 mg) if wife is HBsAg-negative. <i>More remote contact</i> —No action.	Treat as if not pregnant. 500 mg normal immunoglobulin. No action.
(3) Chronic hepatitis Treat infant as if mother had acute hepatitis at term.	No action (? no risk transmission to infant).
(4) Hepatitis carrier No action. Follow infant for 1 year.	—
(5) Previous infant neonatal hepatitis If mother HBsAg-positive treat infant with specific immunoglobulin as above.	Look for non-infective causes.

clustering of hepatitis B infections is well recognized in some communities (Ohbayashi, Okochi and Majumi, 1972; Mazzur, Blumberg and Frielaender, 1974) and circumstantial evidence suggests that a carrier mother is often the source of infection. However, transplacental transmission does not occur often enough to account for the number of adult carriers in Western Europe or North America. It may well be the major factor in other countries such as Taiwan (Stevens *et al.*, 1975) while in yet other areas children who are chronic carriers frequently present with non-hepatic manifestations of 'immune complex disease' such as glomerulonephritis (Brozosko *et al.*, 1974). The factors responsible for these differences in response are unknown.

The management of individual patients presents problems which are summarized in Table 5. The infant born to a mother with acute hepatitis B near term is clearly at risk of infection and the administration of specific hepatitis B immunoglobulin to these infants should be considered. Half the adult dose has been used (Fawaz *et al.*, 1975; Kohler *et al.*, 1974; Cossart and Cohen, 1976) but its efficacy in these circumstances is unproved. It is often convenient to separate mother and infant until the mother's hepatitis subsides, but post-natal exposure by personal contact or because the milk contains

HBsAg (Boxall, 1975) is likely to be trivial compared with that during delivery.

The mother with acute hepatitis is better isolated since it will seldom be known whether she has hepatitis A or B when she is admitted. Carriers in England seldom transmit to their infants so a policy of non-intervention seems best for the group. Routine screening of pregnant women for HBsAg cannot be justified as a preventive measure, and separation of mother and infant is misguided when it is unlikely that the mother will become HBsAg-negative within a foreseeable time. There is no evidence that breast feeding is a significant factor in transmitting hepatitis B to the infants of carriers (Beasley *et al.*, 1975) and its prohibition is probably unnecessary.

The actual delivery of HBsAg-positive patients may present hazards to the staff. The main risk is from accidental inoculation with a blood-stained needle and the general hospital policy should include arrangements for the routine reporting of all such incidents so that specific immunoglobulin can be offered whenever it is warranted.

Apart from this, the main problem is the laundry and it is certainly advisable to send all the patient's bed linen to the hospital 'soiled wash'. It is convenient for the nursing staff if a single room is available

so that the infant can remain 'rooming in' with the mother. After they go home the room should be cleaned with a dilute chlorine-based disinfectant but more rigorous measures are unnecessary.

In this context it is important to remember that every maternity ward will deal with far more unrecognized carriers than those identified by a chance HB_sAg test. If the general routine is satisfactory there will be no need to provide specific facilities for known carriers.

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