The Effects of Hepatitis A and B in Pregnancy on Mother and Fetus

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SUMMARY

A woman who developed hepatitis B during the 3rd trimester of pregnancy gave birth to a preterm, small-for-gestational-age infant whose blood also contained hepatitis B antigen. The effects of viral hepatitis on the fetus are reviewed and an approach to the management of such pregnancies is formulated.


Hepatitis A or B during pregnancy is uncommon. When it does occur, what effects can it have on the mother and her infant? In an attempt to answer this question we report a relevant case and review current knowledge.

CASE REPORT

A 29-year-old mother, with 2 healthy children, was found to be jaundiced at a routine antenatal clinic visit. She was thought to be 28 weeks pregnant at that time. Radioimmunoassay was positive for hepatitis B surface antigen (HBsAg) and she was admitted to a hospital for infectious diseases. Two days later she went into premature labour and a baby girl weighing 1 450 g was delivered. The infant's age was assessed at 33 weeks, making her small for gestational age. Three days after delivery, blood from the baby was found to be positive for HBsAg. The child remained in hospital for 55 days and had an uncomplicated course. When she was discharged her weight was 2 160 g and head circumference was 32 cm, both below the 10th centile. There was no clinical or biochemical evidence of liver dysfunction.

The mother had had an uncomplicated attack of HBsAg-positive hepatitis late in pregnancy. This possibly precipitated the delivery of a small-for-gestational-age preterm infant. The infant's blood was found to be HBsAg-positive on the 3rd day. This implied transplacental rather than postnatal transmission of the hepatitis B virus (HBV) or its surface antigen markers. The infant remained well but the ultimate prognosis was guarded.

Hepatitis A (infectious hepatitis) is the commonest form of jaundice in pregnancy. In countries where sophisticated medical care is available, hepatitis during pregnancy does not cause an increase in mortality rates. Where this is not the case, the mortality may be higher, with a more severe form of hepatitis. The difference is usually attributed to the nutritional state of the mother. The fetus is unaffected and is usually born prematurely. The newborn is at risk of infection if the mother has acute hepatitis late in pregnancy or in the puerperium.

Hepatitis B (serum hepatitis) in pregnancy is a more complex problem in that the fetus is at risk of developing HBV infection. This article reviews the evidence and developments which have a direct bearing on the transmission of HBV infection from mother to baby.

The initial discovery of the Australia antigen by Blumberg et al. and its subsequent specific association with hepatitis B virus reported by Prince, have been followed by discoveries of new components of hepatitis B antigens. The story is not yet complete. Under the electron microscope the antigen displays three morphological forms: (i) small spherical particles; (ii) filamentous forms; and (iii) larger, more complex particles (Dane particles).

The spherical and tubular particles are most numerous in the blood during acute and chronic HBV infection. (They do not contain nucleic acid and are not complete virions, but are more likely to be incomplete non-infectious virus-coated particles.)

The Dane particle has properties characteristic of a virus. It is a complex double-layered structure with an outer coat and inner core containing a unique antigen, a DNA polymerase and small double-stranded circular DNA that serves as a primer template for the DNA polymerase. The World Health Organization Committee has recently officially equated the HBV with the Dane particle. If it is the complete virus, it does not belong to any known group and represents a new class of virus. The ultrastructure of the Dane particle indicates the possibility that a second virus, a helper virus, as yet not identified, may be required for Dane particle replication.

Dane particles occur in high concentration during the incubation period and during acute infection, but in most carriers the concentration is low. However, 1 in 10-20 carriers has a very high level of Dane particle polymerase activity. These carriers, when pregnant, are as much of a risk to their babies as a mother with an acute infection.
At the present time, three antigen/antibody systems associated with hepatitis B have been identified:

1. **HBsAg** located on the surface of the small spherical and filamentous forms as well as on the surface of the Dane particle. The antibody is designated anti-HBs and correlates with immunity to the HBV.8

2. Hepatitis B core antigen (HBcAg) which is present in the core of the Dane particle. The corresponding antibody is anti-HBc.

3. Hepatitis B e antigen (HBeAg) described in 19728 together with its antibody (anti-HBe). It is a soluble serum component distinct from the Dane particle and is found exclusively in HBsAg-positive sera. The detection of e antigen in a pregnant woman indicates that there is a high degree of risk that she will infect her baby.9 Recently, Vyas et al.10 demonstrated an abnormal isoenzyme LDH-Sex which has the antigenic specificity of the HBeAg.11 This may represent liver damage caused by the virus.

**Effect of Hepatitis on a Pregnant Mother**

Available evidence suggests that hepatitis has no adverse effect on the course of pregnancy in the mother.1 However, mothers acutely or chronically ill with hepatitis B often go into premature labour.12

**Transmission of HBV to the Fetus**

Transmission of HBV to the fetus will depend on whether the mother has the primary acute hepatitis during the last trimester or whether she is a chronic carrier. Children born to asymptomatic carriers of HBsAg are much less likely to become infected than those whose mothers develop acute hepatitis late in pregnancy.13 Possible explanations for this include higher infectious HBV titres in sera from mothers with acute hepatitis, unknown HBV virulence factors and the absence of unspecified maternal substances (which normally provide some level of passive protection to the infant) from the sera of mothers with acute hepatitis.14

**Acute hepatitis.** Transmission of HBV takes place more commonly if the acute hepatitis occurs during the last trimester or in the postpartum period. During this phase, 70% of infants become chronic carriers of the antigen, which confirms actual transmission of the virus to the infant rather than simply transmission of antigenic markers for HBV.15 Transmission may occur across the placenta, but more often occurs by direct contact with HBsAg-contaminated maternal serum, because most infants become seropositive about 6 weeks after birth. On the other hand, those women who have the acute illness during the early stages of pregnancy do not give birth to infants who develop chronic antigenaemia. This is thought to be related to placental transfer of antibodies against HBV to infants, thus preventing transmission and proliferation of HBV in utero or after delivery.16 Other possible reasons include failure of the virus to cross the placenta during the early stages, or failure of the fetus during the early stages to support replication of the HBV.17

**Chronic carriers.** In this important group there is usually no history of hepatitis, and there is little or no evidence of liver damage, but there is persistent production of HBsAg with minimal synthesis of anti-HBs and minimal cellular response. These women are impossible to detect except by screening. Okada et al.18 found that neonatal transmission of HBV occurred from 10 asymptomatic chronic HBsAg-carrier mothers who had e antigen but in none of 7 mothers with anti-e antibodies. They also detected Dane particles in the serum of all mothers with e antigen and in none with e antibody, suggesting that the presence of both e antigen and Dane particle in the serum of chronic carriers is important for the transmission of infection. Antibody to HBe is associated with protection of the fetus. This is not always true since Gerety and Schweitzer19 report 2 mothers with e antibody who transmitted HBV to their offspring.

The incidence of transmission by mothers who are chronic carriers varies greatly, occurring less commonly in Western countries (5 of 14 in the USA,20 and 0 of 28 in Denmark21) as compared with Asian countries (12 of 23 in Japan22 and 63 of 158 in Taiwan23). Similar figures are not available for local population groups in South Africa.

**Chronic hepatitis.** Most patients who have HBV infection develop adequate protective antibodies and will become HBsAg-negative. Occasionally hepatitis B infection may lead to chronic antigenaemia with ongoing evidence of liver disease. These patients can be more easily identified during pregnancy and the risk to the fetus is similar to that of the chronic asymptomatic carrier of HBsAg.

**Mode of Transmission of HBV from Mother to Infant**

Despite numerous studies, the exact mode of transmission of HBV from mother to infant remains unclear. Infection may occur in utero, when the amniotic fluid and/or cord blood are positive for HBsAg.24 More frequently, infection occurs during delivery or during the first few days after birth, and antigenaemia usually appears about the 6th week of life.25 This may either be via maternofetal transfusion during labour or by oral ingestion of contaminated blood during passage through the birth canal.26 There is also opportunity for transmission during the postnatal period via menstrual blood, breast milk and saliva.

HBsAg has been detected in cord serum without subsequent evidence of active infection.27 This either represents a false-positive test or the infants do not support HBV replication. They may be passively protected by maternal substances as yet unknown, or may lack the enzymes, metabolites or helper viruses needed to produce HBV infection.28

**Response of Neonates to HBV Exposure**

Infants born to mothers who are acutely ill or chronic carriers of hepatitis B run a high risk of becoming infected with HBV. When infected they may respond in one of three ways:
Acute hepatitis. The majority of infants recover with the production of antibody. A small number develop chronic hepatitis or die in the acute phase.21

Chronic antigenaemia without liver disease. Some of these infants will be clear of antigen during the 2nd or 3rd year of life while others seem to have been rendered tolerant because the virus is transmitted at a time when their immune mechanisms are incompletely developed.22

Chronic antigenaemia with subclinical hepatitis. This is detected by liver biopsy. It is in this group that there is much concern since increasing evidence suggests an ominous long-term prognosis.23 These asymptomatic HBsAg-positive infants may have histological evidence of hepatic necrosis despite minimal clinical or laboratory evidence of disease.24 These infants may have an increased incidence of chronic liver disease, cirrhosis and ultimate hepatic failure.25 However, more long-term prospective studies are needed to define the nature of the problem.

MANAGEMENT

Hepatitis A

If a pregnant mother is exposed to hepatitis A virus, passive immunization with immune serum globulin has consistently prevented clinical hepatitis in the mother.26 When this form of hepatitis occurs during labour or in the puerperium, it has not yet been fully investigated whether the infant should receive gammaglobulin or be separated from its mother. We recommend that in this situation the infant be given prophylactic gammaglobulin and remain with the mother.

Hepatitis B

Screening of mothers. It may be suggested that because carriers can be asymptomatic, all pregnant women should be screened. This will be worth while only if there is effective prophylaxis against HBV infection for the neonate. Limited evidence suggests this can be achieved by passive immunization of newborn babies with hyperimmune hepatitis B globulin.27 The incidence of HBsAg-positive sera of blood donors in Cape Town is 18/1000 (D. Fitzgerald — personal communication), and the ergonomics of examining 18 000 antenatal samples of serum annually to detect 324 positive sera may be impractical.

Prevention of infection. Therapy is unlikely to prevent transplacental transmission whereas passive immunization of the newborn baby is claimed to be highly effective in preventing HBV transmission. Kohler et al.27 treated 4 infants of HBsAg-positive mothers with hyperimmune globulin within 1 - 6 days of birth and found that they were all HBsAg-negative at 5 - 14 months. Six of the 7 infants in the group who received no therapy became HBsAg-positive within 5 - 12 weeks, and the antigenaemia persisted in all infants for up to 3 years.

If HBV infection has occurred antenatally, passive antibody therapy to the infant would be contraindicated, since antibody does not affect established infection and toxic immune-complex formation can occur.27 Such reactions have not been observed and therefore hyperimmune globulin is considered to be safe.28 It should, however, not be given if the cord blood is positive for HBsAg.

Breast feeding. The hepatitis B antigen may be present in breast milk and serum exuding from cracked or irritated nipples.29 Because of this, Krugman30 stated that breast feeding should be avoided if mothers are HBsAg-positive.

A recent study,31 however, has concluded that the role of breast feeding in mother-to-infant transmission of HBsAg is unimportant. Among 17 carrier infants, only 4 (3 of whom had HBsAg-positive cord blood) were breast-fed, whereas 28 of 64 infants who were antigen-negative were breast-fed for varying periods. We therefore agree with Derso et al.32 that mothers who are HBsAg-positive should not be discouraged from breast-feeding their babies.

Suggested Management

All mothers should be screened for HBsAg during pregnancy. If the pregnant woman is HBsAg-positive, blood should be examined late in pregnancy, i.e. in the 36th week, for the presence of e antigen. In all babies born to HBsAg-positive mothers, cord blood should be examined for the presence of HBsAg. If the cord blood is positive for HBsAg, no active treatment is indicated, but adequate follow-up is essential. If the cord blood is negative for HBsAg and the mother is e antigen-positive or e antibody-negative at 36 weeks, the baby should receive hyperimmune globulin within 7 days of birth. If the mother is e antibody-positive, then, according to Okada et al.,33 there is no need to treat the baby. However, this concept has been questioned by Gerety and Schweitzer.34

The relative insensitivity of available tests for e antigen and antibody detection makes conclusions with regard to their roles in neonatal HBV infections somewhat premature. Because of this, and since passive immunization for hepatitis B is considered to be safe, we would suggest that all infants born to mothers with HBsAg at the time of delivery, and who are HBsAg-negative, be treated with hyperimmune gammaglobulin.

CONCLUSION

Hepatitis A during pregnancy carries no risk to mother or fetus, apart from prematurity, but we recommend that the infant be given gammaglobulin if hepatitis occurs late in pregnancy, during labour or in the puerperium. Acute hepatitis B in the last trimester has a 70% risk of transmission of HBV to the fetus. The risk of HBV transmission is much lower if hepatitis occurs early in pregnancy or in mothers who are chronic carriers. The infant who receives HBV from its mother may develop (i) acute hepatitis, which is rare; (ii) chronic subclinical hepatitis, which is more common; or (iii) a chronic carrier state without evidence of liver disease.

HBV infection in infants of HBsAg-positive mothers may be prevented with hyperimmune globulin, but further studies are needed to confirm this.
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REFERENCES


Fractures and Dislocations of the Ankle Joint

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SUMMARY

The classification of fractures of the ankle joint is based on the mechanism of injury, which provides the clue to successful reduction. The physiological movements of the ankle and foot are defined, and the pathological movements associated with injury are described.


'Without theory, practice is but a routine born of habit. Theory alone can bring forth and develop the spirit of invention'.

L. Pasteur

There are many bones of contention, and almost as many classifications of injury as there are bones in the ankle and foot. The problems are not far to seek, first among them the basis of the classification. We reject an anatomical basis as practically unsound, and we believe that only those classifications which are based on the mechanism of injury can and should survive. The three major contributors in this respect have been Ashhurst and Bromer,3 Bonnin,2 and Lauge-Hansen.2-3 For reasons described below, we advise and indeed use the classification of Bonnin.2

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Other problems are terminology on the one hand, and the complicated movements of the foot relative to the leg on the other. In these movements, both normal and forced, the ankle joint, the subtaloid joint and the midtarsal joint are all involved in varying degrees. Unless and until uniformity and unanimity of terminology are achieved, confusion and ambiguity will persist. (Stated more simply, the movements of the ankle, the hindfoot and the forefoot must be considered.)

In the past, there were those who made their contributions. Notable among the early workers were Percival Pott (1714 - 1788), Sir Astley Cooper (1768 - 1841), both of England, Dupuytren (1777 - 1835), Maisonneuve (1809 - 1897) and Destot of France, Ashhurst and Bromer of the USA and many others. 'Destot's book Traumatismes du Pied et Rayons-X, published in 1911, was the first monograph in which the evidence provided by radiography (discovered by Roentgen in 1895) was considered. This book still remains the French authority ... ' The myth of Pott's fracture survives to the present day.

WHAT IS POTT'S FRACTURE?

Percivall Pott1 was the first major British surgeon to publish his views on ankle fractures. He wrote the article while convalescing from a fractured tibia and fibula. He did not himself suffer from 'Pott's' fracture. Misunderstanding has arisen, some no doubt due to the comment of Ashhurst and Bromer2 who wrote: 'Pott (1768) described a fracture which does not exist, and Dupuytren (1819) commended him for his acute observation and fidelity to