

Hepatitis in pregnancy: Sorting through the alphabet

This common viral infection may pose a danger to the pregnant woman as well as to the fetus and newborn. Here, expert diagnosis and management pearls for the types of hepatitis that may be encountered in a pregnant patient.

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CASE Pregnant woman with positive hepatitis B surface antigen

A 27-year-old primigravida at 9 weeks 3 days of gestation tests positive for the hepatitis B surface antigen at her first prenatal appointment. She is completely asymptomatic.

- What additional tests are indicated?
- Does she pose a risk to her sexual partner, and is her newborn at risk for acquiring hepatitis B?
- Can anything be done to protect her partner and newborn from infection?

Meet our perpetrator

Hepatitis is one of the more common viral infections that may occur during pregnancy. Two forms of hepatitis, notably hepatitis A and E, pose a primary threat to the mother. Three forms (B, C, and D) present dangers for the mother, fetus, and newborn. This article will review the epidemiology, clinical manifestations, perinatal implications, and

management of the various forms of viral hepatitis. (TABLE 1, page 30).

Hepatitis A

Hepatitis A is caused by an RNA virus that is transmitted by fecal-oral contact. The disease is most prevalent in areas with poor sanitation and close living conditions. The incubation period ranges from 15 to 50 days. Most children who acquire this disease are asymptomatic. By contrast, most infected adults are acutely symptomatic. Clinical manifestations typically include low-grade fever, malaise, anorexia, right upper quadrant pain and tenderness, jaundice, and clay-colored stools.^{1,2}

The diagnosis of acute hepatitis A infection is best confirmed by detection of immunoglobulin M (IgM)-specific antibodies. The serum transaminase concentrations and the serum bilirubin concentrations usually are significantly elevated. The international normalized ratio, prothrombin time, and partial thromboplastin time also may be elevated.^{1,2}

The treatment for acute hepatitis A largely is supportive care: maintaining hydration, optimizing nutrition, and correcting coagulation abnormalities. The appropriate measures for prevention of hepatitis A are adoption of sound sanitation practices, particularly water purification; minimizing overcrowded living conditions; and administering the hepatitis A vaccine for both pre and postexposure prophylaxis.^{3,4} The hepatitis

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TABLE 1 Summary of key features of viral hepatitis in pregnancy

Infection	Nucleic acid	Best diagnostic test	Perinatal transmission	Immunoprophylaxis
A	RNA	Antibody detection	Rare	Hepatitis A vaccine
B	DNA	Detection of surface antigen PCR	Common in absence of immunoprophylaxis	HBIG and hepatitis B vaccine
C	RNA	Antibody detection PCR	Uncommon unless patient is coinfecting with HIV	None
D	RNA	Antigen and antibody detection	May occur in association with transmission of hepatitis B	Prophylaxis for hepatitis B protects against hepatitis D
E	RNA	Antibody detection PCR	Rare	Hepatitis E vaccine
G	RNA	Antibody detection	Yes, but no clinical significance	None

Abbreviations: PCR, polymerase chain reaction; HBIG, hepatitis B immune globulin.

A vaccine is preferred over administration of immune globulin because it provides lifelong immunity.

The hepatitis A vaccine is produced in 2 monovalent formulations: Havrix (Glaxo-SmithKline) and Vaqta (Merck & Co, Inc). The vaccine should be administered intramuscularly in 2 doses 6 to 12 months apart. The wholesale cost of the vaccine varies from \$66 to \$119 (according to <http://www.goodrx.com>). The vaccine also is available in a bivalent form, with recombinant hepatitis B vaccine (Twinrix, GlaxoSmithKline). When used in this form, 3 vaccine administrations are given—at 0, 1, and 6 months apart. The cost of the vaccine is approximately \$150 (according to <http://www.goodrx.com>). **TABLE 2** (page 31) lists the individuals who are appropriate candidates for the hepatitis A vaccine.^{3,4}

Hepatitis B

Hepatitis B is caused by a DNA virus that is transmitted parenterally or perinatally or through sexual contact. Four genotypes have been identified: A, B, C, and D.

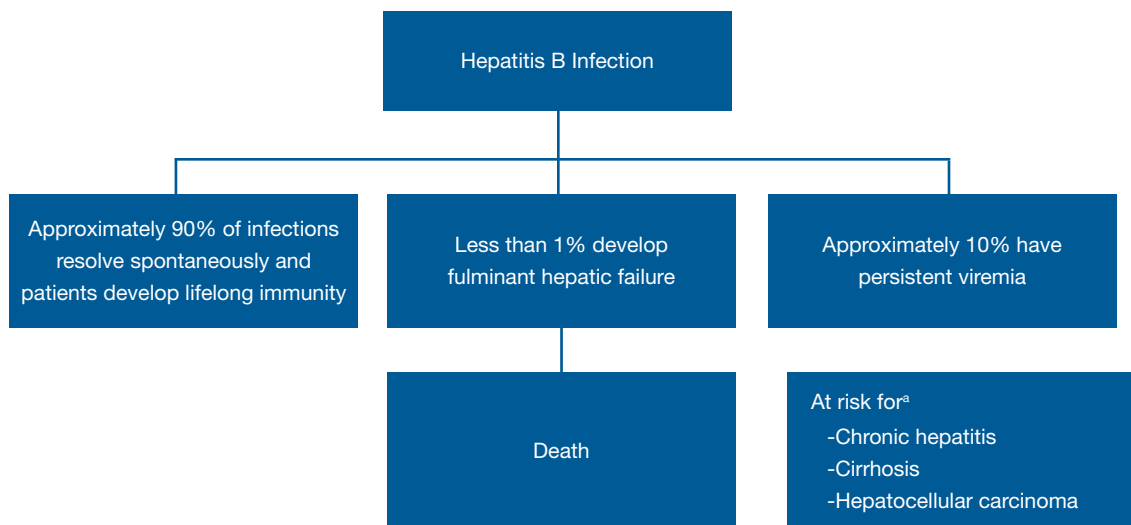
Acute hepatitis B affects 1 to 2 of 1,000 pregnancies in the United States. Approximately 6 to 10 patients per 1,000 pregnancies are asymptomatic but chronically infected.⁴ The natural history of hepatitis B infection is shown in the **FIGURE**. The diagnosis of acute and chronic hepatitis B is best established by serology and polymerase chain reaction (PCR; **TABLE 3**, page 32).

All pregnant women should be routinely screened for the hepatitis B surface antigen.^{5,6} If they are seropositive for the surface antigen alone and receive no immunoprophylaxis, they have a 20% to 30% risk of transmitting infection to their neonate. Subsequently, if they also test positive for the hepatitis Be antigen, the risk of perinatal transmission increases to approximately 90%. Fortunately, 2 forms of immunoprophylaxis are highly effective in preventing perinatal transmission. Infants delivered to seropositive mothers should receive hepatitis B immune globulin within 12 hours of birth. Prior to discharge, the infant also should receive the first dose of the hepatitis B vaccine. Subsequent doses should be administered at 1 and

TABLE 2 Candidates for the hepatitis A vaccine^{3,4}

- Children who reside in endemic areas
- Intravenous drug users
- International travelers
- Persons with chronic liver disease
- Persons with clotting factor disorders who require periodic infusions of coagulation blood products
- Persons with occupational exposure (eg, workers in a primate laboratory)
- Residents and staff of chronic care facilities

FIGURE Natural history of hepatitis B infection¹



^a These sequelae are particularly likely if the patient is coinfecting with hepatitis D.

6 months of age. Infants delivered to seronegative mothers require only the vaccine series.¹

Although immunoprophylaxis is highly effective, some neonates still acquire infection perinatally. Pan and colleagues⁷ and Jourdain et al⁸ demonstrated that administration of tenofovir 200 mg orally each day from 32 weeks' gestation until delivery provided further protection against perinatal transmission in patients with a high viral load (defined as >1 million copies/mL). In 2016, the Society for Maternal-Fetal Medicine endorsed the use of tenofovir in women with a high viral load.⁶

Following delivery, women with chronic hepatitis B infection should be referred to a

hepatology specialist for consideration of direct antiviral treatment. Multiple drugs are now available that are highly active against this micro-organism. These drugs include several forms of interferon, lamivudine, adefovir, entecavir, telbivudine, and tenofovir.¹

Hepatitis C

Hepatitis C is caused by an RNA virus that has 6 genotypes. The most common genotype is HCV1, which affects 79% of patients; approximately 13% of patients have HCV2, and 6% have HCV3.⁹ Of note, the 3 individuals who discovered this virus—Drs. Harvey Alter, Michael Houghton, and Charles Rice—received the 2020 Nobel Prize in Medicine.¹⁰

TABLE 3 Serologic profiles of hepatitis B infection¹

Clinical scenario	PCR	HBsAg	HBsAb	HBcAb	HBeAg
Susceptible	-	-	-	-	-
Acute infection	+	+	-	+ IgM	+ / - ^a
Chronic infection	+	+	-	+ IgG	+ / - ^a
Immune from natural infection	-	-	+	+ IgG	-
Immune from vaccination	-	-	+	-	-

Abbreviations: PCR, polymerase chain reaction; HBsAg, hepatitis B surface antigen; HBsAb, antibody to the surface antigen; HBcAb, hepatitis B core antibody; HBeAg, hepatitis Be antigen.

^aPresence of HBeAg implies high rate of viral replication and high level of infectivity. Most patients do not harbor the e antigen.

FAST TRACK

Routine screening for hepatitis C in pregnancy is now recommended given the seriousness of the infection and the disease's increasing prevalence

Hepatitis C is transmitted via sexual contact, parenterally, and perinatally. In many patient populations in the United States, hepatitis C is now more prevalent than hepatitis B. Only about half of all infected persons are aware of their infection. If patients go untreated, approximately 15% to 30% eventually develop cirrhosis. Of these individuals, 1% to 3% develop hepatocellular cancer. Chronic hepatitis C is now the most common indication for liver transplantation in the United States.^{1,9}

In the initial stages of infection, hepatitis C usually is asymptomatic. The best screening test is detection of hepatitis C antibody. Because of the increasing prevalence of this disease, the seriousness of the infection, and the recent availability of remarkably effective treatment, routine screening, rather than screening on the basis of risk factors, for hepatitis C in pregnancy is now indicated.^{11,12}

The best tests for confirmation of infection are detection of antibody by enzyme immunoassay and recombinant immunoblot assay and detection of viral RNA in serum by PCR. Seroconversion may not occur for up to 16 weeks after infection. Therefore, in at-risk patients who initially test negative, retesting is advisable. Patients with positive test results should have tests to identify the specific genotype, determine the viral load, and assess liver function.¹

In patients who have undetectable viral loads and who do not have coexisting HIV infection, the risk of perinatal transmission of hepatitis C is less than 5%. If HIV infection is present, the risk of perinatal transmission approaches 20%.^{1,13,14}

If the patient is coinfecting with HIV, a scheduled cesarean delivery should be performed at 38 weeks' gestation.¹ If the viral load is undetectable, vaginal delivery is appropriate. If the viral load is high, however (arbitrarily defined as >2.5 million copies/mL), the optimal method of delivery is controversial. Several small, nonrandomized noncontrolled cohort studies support elective cesarean delivery in such patients.¹⁴

There is no contraindication to breastfeeding in women with hepatitis C unless they are coinfecting with HIV. In such a circumstance, formula feeding should be chosen. After delivery, patients with hepatitis C should be referred to a gastroenterology specialist to receive antiviral treatment. Multiple new single-agent and combination regimens have produced cures in more than 90% of patients. These regimens usually require 8 to 12 weeks of treatment, and they are very expensive. They have not been widely tested in pregnant women.¹

Hepatitis D

Hepatitis D, or delta hepatitis, is caused by an RNA virus. This virus is unique because it is incapable of independent replication. It must be present in association with hepatitis B to replicate and cause clinical infection. Therefore, the epidemiology of hepatitis D closely mirrors that of hepatitis B.^{1,2}

Patients with hepatitis D typically present in one of two ways. Some individuals are acutely infected with hepatitis D at the same time that they acquire hepatitis B (coinfection). The natural history of this infection

usually is spontaneous resolution without sequelae. Other patients have chronic hepatitis D superimposed on chronic hepatitis B (superinfection). Unfortunately, patients with the latter condition are at a notably increased risk for developing severe persistent liver disease.^{1,2}

The diagnosis of hepatitis D may be confirmed by identifying the delta antigen in serum or in liver tissue obtained by biopsy or by identifying IgM- and IgG-specific antibodies in serum. In conjunction with hepatitis B, the delta virus can cause a chronic carrier state. Perinatal transmission is possible but uncommon. Of greatest importance, the immunoprophylaxis described for hepatitis B is almost perfectly protective against perinatal transmission of hepatitis D.^{1,2}

Hepatitis E

Hepatitis E is an RNA virus that has 1 serotype and 4 genotypes. Its epidemiology is similar to that of hepatitis A. It is the most common waterborne illness in the world. The incubation period varies from 21 to 56 days. This disease is quite rare in the United States but is endemic in developing nations. In those countries, maternal infection has an alarmingly high mortality rate (5%–25%). For example, in Bangladesh, hepatitis E is responsible for more than 1,000 deaths per year in pregnant women. When hepatitis E is identified in more affluent countries, the individual cases and small outbreaks usually are linked to consumption of undercooked pork or wild game.^{1,15–17}

The clinical presentation of acute hepatitis E also is similar to that of hepatitis A. The usual manifestations are fever, malaise, anorexia, nausea, right upper quadrant pain and tenderness, jaundice, darkened urine, and clay-colored stools. The most useful diagnostic tests are serologic detection of viral-specific antibodies (positive IgM or a 4-fold increase in the prior IgG titer) and PCR-RNA.^{1,17}

Hepatitis E usually does not cause a chronic carrier state, and perinatal transmission is rare. Fortunately, a highly effective

vaccine was recently developed (Hecolin, Xiamen Innovax Biotech). This recombinant vaccine is specifically directed against the hepatitis E genotype 1. In the initial efficacy study, healthy adults aged 16 to 65 years were randomly assigned to receive either the hepatitis E vaccine or the hepatitis B vaccine. The vaccine was administered at time point 0, and 1 and 6 months later. Patients were followed for up to 4.5 years to assess efficacy, immunogenicity, and safety. During the study period, 7 cases of hepatitis E occurred in the vaccine group, compared with 53 in the control group. Approximately 56,000 patients were included in each group. The efficacy of the vaccine was 86.8% ($P<.001$).¹⁸

Hepatitis G

Hepatitis G is caused by 2 single-stranded RNA viruses that are virtually identical—hepatitis G virus and GB virus type C. The viruses share approximately 30% homology with hepatitis C virus. The organism is present throughout the world and infects approximately 1.5% to 2.0% of the population. The virus is transmitted by blood and sexual contact. It replicates preferentially in mononuclear cells and the bone marrow rather than in the liver.^{19–21}

Hepatitis G is much less virulent than hepatitis C. Hepatitis G often coexists with hepatitis A, B, and C, as well as with HIV. Coinfection with hepatitis G does not adversely affect the clinical course of the other conditions.^{22,23}

Most patients with hepatitis G are asymptomatic, and no treatment is indicated. The virus can cause a chronic carrier state. Perinatal transmission is distinctly uncommon. When it does occur, however, injury to mother, fetus, or neonate is unlikely.^{1,24}

The diagnosis of hepatitis G can be established by detection of virus with PCR and by the identification of antibody by enzyme immunoassay. Routine screening for this infection in pregnancy is not indicated.^{1,2}

CASE Resolved

Hepatitis B is highly contagious and can be transmitted from the patient to her sexual partner and

FAST TRACK

Although rare in the United States, maternal infection of hepatitis E has a mortality rate of up to 25%

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neonate. Testing for hepatitis B surface antigen and antibody is indicated in her partner. If these tests are negative, the partner should immediately receive hepatitis B immune globulin and then be started on the 3-dose hepatitis B vaccination series. The patient's newborn also should receive hepatitis B immune globulin within 12 hours of delivery and should receive the first dose of the hepatitis B vaccine prior to discharge from the hospital. The second and third doses should be administered 1 and 6 months after delivery.

The patient also should have the following tests:

- liver function tests

- serum transaminases
- direct and indirect bilirubin
- coagulation profile

- hepatitis D antigen
- hepatitis B genotype
- hepatitis B viral load
- HIV serology.

If the hepatitis B viral load exceeds 1 million copies/mL, the patient should be treated with tenofovir 200 mg daily from 28 weeks' gestation until delivery. In addition, she should be referred to a liver disease specialist after delivery for consideration of treatment with directly-acting antiviral agents. ●

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