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CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

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Viral Hepatitis in Pregnancy

Viral hepatitis is one of the most common and potentially serious infections that can occur in pregnant women. Six forms of viral hepatitis have now been identified, two of which, hepatitis A and hepatitis B, can be prevented effectively through vaccination. The purpose of this document is to describe the specific subtypes of hepatitis, their implications during pregnancy, the risk of perinatal transmission, and issues related to both treatment and prevention of infection.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Neil S. Silverman, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Background

Hepatitis A

The hepatitis A virus is a small (27 nm) RNA virus that produces either symptomatic or asymptomatic infection in humans after an average incubation period of 28 days (range, 15–50 days). Hepatitis A virus (HAV) replicates within the liver and is excreted in bile, with highest viral concentrations late in the incubation period in the feces; this represents the window of greatest infectivity.

In the prevacccine era, approximately one third of cases of acute hepatitis in the United States were attributable to HAV infection. Person-to-person transmission through fecal–oral contamination is the primary means of HAV infection in the United States, most often in household and extended family settings (1). Because children usually have asymptomatic or unrecognized infection, they can play a key role in infecting others. Studies have demonstrated that up to 40% of adults without an identifiable source of infection had close contact with a child younger than 6 years (2), which underscores the importance of primary HAV prevention within families of women of reproductive age.

Poor hygiene and poor sanitation can result in common-source outbreaks of HAV infection. Food also can be contaminated after cooking, as commonly occurs in outbreaks associated with HAV-infected food handlers whose hygiene practices are substandard (3). Depending on conditions, HAV can be stable in

the environment for months. Heating foods to above 185°F for 1 minute or disinfecting surfaces with a dilute solution of household bleach can inactivate the virus.

Serious complications of HAV infection are uncommon; the overall case–fatality ratio among reported cases is less than 1%, but reaches 2% among adults older than 50 years. Hepatitis A does not lead to chronic infection, although 10–15% of symptomatic individuals can have prolonged or relapsing disease lasting up to 6 months (4).

Hepatitis B

Hepatitis B is caused by a small DNA virus. The intact virus is termed the Dane particle. Hepatitis B virus (HBV) contains three principal antigens. Hepatitis B surface antigen (HBsAg) is present on the surface of the virus and circulates freely in the serum in spherical and filamentous forms. The middle portion of the Dane particle contains hepatitis B core antigen (HBcAg). The core antigen is present only in hepatocytes and does not circulate in the serum. Hepatitis B e antigen (HBeAg) is encoded by the same portion of the viral genome that codes for the core antigen. The presence of HBeAg indicates an extremely high viral inoculum and active virus replication.

Hepatitis B virus is transmitted by parenteral and sexual contact. Although HBsAg has been detected in a variety of body fluids, only serum, semen, and saliva have been proved to be infectious (5, 6). The virus is relatively stable in the environment, can be viable for up to 7 days on surfaces at room temperature, and may cause transmission via surfaces at concentrations of only 10^2–10^3 virions per milliliter, even if there is no visible blood (7). Individuals at greatest risk of becoming infected are those who have multiple sexual partners, inject drugs percutaneously, or have sexual partners who engage in these risk-taking behaviors. Sexual contact is an efficient mechanism for spreading the virus. Approximately 25% of the frequent sexual contacts of infected individuals will themselves become infected (8).

All blood donors are screened routinely for HBsAg. Transmission of HBV by transfusion of blood or blood products is rare as a result of both donor screening and blood banking viral inactivation procedures. Recently, it has been estimated that the risk of transfusion-attributable HBV infection is 1 per 137,000 transfused units of screened blood (9, 10). In contrast, however, HBV transmission has been reported via patient-to-patient use of institution-based fingerstick devices for blood sampling, such as blood glucose meters (11). Appropriate attention to hygiene and universal precautions is critical within households and institutions using such devices (12).

The mortality associated with acute hepatitis B is approximately 1%. Of adult patients who become infected, 85–90% experience complete resolution of their physical findings and develop protective levels of the antibody. The other 10–15% of patients become chronically infected. They continue to have detectable serum levels of HBsAg but are asymptomatic, and most have no biochemical evidence of hepatic dysfunction. In a small subgroup (15–30%) of those chronically infected, viral replication continues and is manifested by persistence of the e antigen and active viral DNA synthesis. These individuals risk subsequent development of chronic or persistent hepatitis and cirrhosis, and approximately 4,000–5,000 die annually of complications of chronic liver disease, including hepatocellular carcinoma (12, 13).

Hepatitis C

At least six distinct hepatitis C virus (HCV) genotypes have been identified, with broad geographic variation and widely ranging prognoses for both disease progression and response to therapy (14). Among presumably low-risk volunteer blood donors in developed countries, rates of HCV seropositivity of 0.5–1.4% have been reported. Groups at higher risk for HCV infection include patients in sexually transmitted disease (STD) clinics (seroprevalence, 1.5–6.2%), hemophiliacs (64–86%), and intravenous drug users (56–86%) (15–17).

The principal risk factors for HCV transmission have been transfusion of blood products and use of intravenous drugs. At least 90% of cases of posttransfusion hepatitis have been traceable to HCV, usually within 5–10 weeks of the transfusion. Mass screening of the blood supply for HCV has markedly decreased the risk of HCV infection to less than 1 per 1,000,000 screened units of blood. Because the risk of HCV infection from blood transfusions has decreased, the number of HCV infections attributable to drug use has significantly increased, from 20% to at least 60% (18).

Acute HCV infection occurs after an incubation period of 30–60 days. Asymptomatic infection occurs in 75% of patients, and at least 50% of infected individuals progress to chronic infection, regardless of the mode of acquisition or severity of initial infection. Chronic HCV infection also has been associated with an increased risk of developing both B-cell lymphomas and cryoglobulinemia. Although at least 20% of chronic HCV infections lead to chronic active hepatitis or cirrhosis, whether a link to hepatocellular carcinoma exists is controversial and may vary by geographic region (19). Hepatitis C and HIV share common transmission routes, and concomitant infection has been reported to accelerate the progression and severity of hepatic injury (18).

Hepatitis D

Hepatitis D virus (HDV) is an incomplete viral particle that causes disease only in the presence of HBV, from

which it acquires a viral envelope consisting entirely of excess HBsAg produced by HBV. Infection with HDV occurs either simultaneously with HBV infection (coinfection) or may be acquired after HBV (superinfection). Transmission is primarily through blood; approximately 20–25% of chronic HBV carriers also have evidence of HDV infection (20, 21).

Chronic hepatitis D produces severe disease more often than other forms of chronic hepatitis. Of patients with chronic hepatitis D, 70–80% ultimately develop cirrhosis and portal hypertension, 15% of whom develop an unusually rapid progression to cirrhosis within 2 years of the initial onset of acute illness. Mortality as a result of hepatic failure approaches 25%. In contrast, only 15–30% of patients with chronic hepatitis B virus infection develop cirrhosis and portal hypertension, and the disease progression typically is much slower (21).

Hepatitis E

The epidemiologic features of hepatitis E virus (HEV) are similar to those of hepatitis A. The disease has been reported only rarely in the United States, and the highest rates of infection occur in regions of the developing world where inadequate sanitation promotes transmission of the virus. Hepatitis E is primarily a waterborne disease; epidemics have been reported in areas where fecal contamination of drinking water is common. The ingestion of raw or undercooked shellfish also has been a source of sporadic cases of HEV infection in endemic areas (22).

In general, HEV produces a self-limited viral infection followed by recovery; the incubation period is 3–8 weeks, with a mean of 40 days. Among pregnant women, however, a higher risk of fulminant hepatitis E has been reported in a number of small series, with maternal mortality rates as high as 20% after infection in the third trimester (22, 23). In one report, HEV infection in women coinfected with HIV resulted in a 100% mortality rate (24).

Vaccinations

Hepatitis A

The hepatitis A vaccination is indicated for adults in groups at increased risk for hepatitis A or its adverse consequences (25). Medical indications include persons with chronic liver disease and persons who receive clotting factor concentrates. Behavioral risk populations are men who have sex with men and persons who use illegal drugs. Occupational risks include persons working with HAV-infected primates or with HAV in a research laboratory setting. Other indications are persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (a list of countries is available at http://www.cdc.gov/travel/diseases.htm) and any person who would like to obtain immunity.

The hepatitis A vaccine is available as both a single-antigen vaccine and as a combination vaccine (containing both HAV and HBV antigens). Both vaccines use inactivated HAV, and the HBV component is a recombinant protein nonviral antigen. There are two HAV vaccines available that are given in two doses, either 6–12 months apart or 6–18 months apart. The combination vaccine is given in three doses at 0, 1, and 6 months. The HAV vaccine is 94–100% immunogenic after the first dose (26) and is highly effective in both reducing disease incidence and interrupting ongoing epidemics (27, 28). Immune globulin remains available for postexposure prophylaxis, although primary vaccine-based prevention is preferred. Hepatitis A vaccination should still be administered in addition to immune globulin even in the context of postexposure prevention. Studies of HAV vaccine alone have shown protection against infection in a limited series (29), although no trials comparing the vaccine with immune globulin have been conducted to date. This strategy of administering HAV vaccine alone for postexposure prophylaxis in individuals younger than 40 years has recently been proposed by some experts.

Hepatitis B

All individuals with risk factors, particularly health care workers, should be vaccinated against HBV infection. Other groups at increased risk include hemodialysis patients, injection drug users, persons with more than one sexual partner during the past 3 months or in whom an STD has been diagnosed recently, clients and staff in centers for the developmentally delayed, and international travelers who will be in high or intermediate prevalence areas for HBV infection (list of countries at http://www.cdc.gov/travel/yellowBookCh4-HepB.aspx#333) (30).

In general, prevaccination testing is not recommended. It may be cost-effective to screen for the antibody to HBV in women who belong to groups with a high risk of infection in order to avoid vaccinating adults who have had or currently have hepatitis B infection. In most other low-risk groups, antibody screening before vaccination probably is not indicated.

Two single antigen vaccines for hepatitis B virus have been developed (Table 1). Currently available vaccines are prepared from yeast cultures by using recombinant DNA technology. They are highly immunogenic and result in seroconversion in more than 95% of recipients. There is one combination vaccine available for adults at risk of both hepatitis A and B virus infection (Twinrix); it contains recombinant HBsAg and inactivated hepatitis A virus. The dosage of the hepatitis A component in the combination

Table 1. Recommended Dosages and Schedules of Single-Antigen Hepatitis B Vaccines

Vaccine	Age Group	Dose	Volume	No. of Doses	Schedule*
Engerix-B† (GlaxoSmithKline)	0–19 y	10 mcg	0.5 mL	3	Infants: birth, age 1–4, 6–18 mo Alternative for older children: 0, 1–2, 4 mo
	20 y and older	20 mcg	1.0 mL	3	0, 1, 6 mo
Recombivax HB‡ (Merck & Co.)	0–19 y	5 mcg	0.5 mL	3	Infants: birth, age 1–4, 6–18 mo Alternative for older children: 0, 1–2, 4 mo
	11–15 y	10 mcg	1.0 mL	2	0, 4–6 mo
	20 y and older	10 mcg	1.0 mL	3	0, 1, 6 mo

*The schedule for hepatitis B vaccination is flexible and varies. Consult the Advisory Committee on Immunization Practices (ACIP) statements on hepatitis B (12/2005 and 12/2006) or the package insert for details.

†For adult dialysis patients, the Engerix-B dose required is 40 mcg/2.0 mL (use the adult 20 mcg/mL formulation) on a schedule of 0, 1, 2, and 6 months.

‡For Recombivax HB, a special formulation for dialysis patients is available. The dose is 40 mcg/1.0 mL and it is given on a schedule of 0, 1, and 6 months.

Immunization Action Coalition. Hepatitis A & B vaccines: be sure your patient gets the correct dose! St. Paul (MN): IAC; 2005. Available at: http://www.immunize.org/catg.d/2081ab.pdf. Retrieved July 20, 2007.

vaccine is lower than that in the single-antigen hepatitis A vaccine, allowing it to be administered in a three-dose schedule (0, 1, and 6 months) instead of the two-dose schedule used for the single-antigen vaccine. An accelerated schedule (0, 7, 21–30 days, followed by a booster dose at 12 months) is an option when a rapid immune response is needed for an occupational or behavioral imminent risk for hepatitis A and B or for international travel (31).

The vaccine should be administered into the deltoid muscle. Intragluteal and intradermal injections result in lower rates of seroconversion. Pregnancy is not a contraindication to vaccination. In fact, susceptible pregnant women who are at risk for HBV infection should be specifically targeted for vaccination (32).

Unvaccinated individuals or persons known not to have responded to a complete hepatitis B vaccine series and who have been exposed to HBV through a discrete, identifiable exposure to blood or to body fluids that contain blood should receive passive immunization with hepatitis B immune globulin (HBIG) and start the immunization series. Immunoprophylaxis should be administered as soon as possible after exposure (preferably within 24 hours). For sexual exposures, HBIG should not be administered more than 14 days after exposure (8).

Clinical Considerations and Recommendations

▶ *What are the clinical manifestations of hepatitis?*

The usual subjective symptoms in patients with acute viral hepatitis are malaise, fatigue, anorexia, nausea, and right upper quadrant or epigastric pain. Typical physical findings include jaundice, upper abdominal tenderness, and hepatomegaly, although many cases of hepatitis are anicteric. The patient's urine usually is darkened, and the stool may be gray or acholic. In cases of fulminant hepatitis, signs of coagulopathy and encephalopathy may be present.

In patients with hepatitis A or E, clinical manifestations usually are related temporally to recent travel to an endemic area or exposure to an infected person. Similarly, infections with hepatitis B, C, or D typically ensue after parenteral exposure to contaminated blood or sexual contact with an infected partner. The evolution of acute clinical illness in patients with hepatitis D often follows a biphasic course. In the initial phase of infection, patients with hepatitis D are indistinguishable from individuals with acute hepatitis B. Two to four weeks after apparent resolution of symptoms, patients typically have a relapse, which usually is of a milder nature and is associated with a second episode of elevation in serum transaminases. At this time serologic assay results for hepatitis D virus usually are positive.

As noted previously, in some patients with acute hepatitis B, C, or D, symptomatic infection resolves, and some become chronic carriers of viral infection. Although most viral hepatitis carriers initially are asymptomatic, up to one third subsequently develop chronic active or persistent hepatitis or cirrhosis. Once cirrhosis ensues, patients have the typical signs of end-stage liver disease, such as jaundice, muscle wasting, ascites, spider angioma, palmar erythema, and, ultimately, hepatic encephalopathy. Hepatitis C is the leading cause of chronic liver disease in the United States, whereas hepatitis B virus is the leading cause worldwide (13, 18).

▶ *How is acute hepatitis managed in pregnant women?*

Patients with acute hepatitis should be hospitalized if they have encephalopathy, coagulopathy, or severe debilitation. Nutritional needs should be addressed within the context of the severity of the disease. Fluid and electrolyte abnormalities should be corrected. If a coagulopathy is present, administration of erythrocytes, platelets, and clotting factors such as fresh frozen plasma or cryoprecipitate may be necessary. Activity should be limited, and the patient should be protected from upper abdominal trauma (32).

Women who are less severely ill may be treated as outpatients. They should reduce their level of activity, avoid upper abdominal trauma, and maintain good nutrition. Infected women also should avoid intimate contact with household members and sexual partners until these individuals receive appropriate prophylaxis (32).

General Tests

Coincident with the onset of symptoms, patients with acute hepatitis usually have a marked increase in the serum concentration of alanine aminotransferase (ALT, previously known as serum glutamate pyruvate transaminase) and aspartate aminotransferase (AST, previously known as serum glutamic oxaloacetic transaminase). In addition, the serum bilirubin concentration often is increased. In patients who are moderately to severely ill, coagulation abnormalities and hyperammonemia also may be present (18). Although liver biopsy is rarely indicated in pregnancy, viral hepatitis may be distinguished histologically from other causes of hepatic injury by its characteristic pattern of extensive hepatocellular injury and inflammatory infiltrate. Initial evaluation of the patient with suspected viral hepatitis should include specific tests.

Specific Tests

If hepatitis is suspected based on the initial evaluation and general tests, the type of virus is determined through laboratory analysis.

Hepatitis A

The diagnosis of acute hepatitis A is confirmed by detecting specific immunoglobulin M (IgM) antibodies to the virus. A chronic carrier state for this infection does not exist, but immunoglobulin G (IgG) antibodies to hepatitis A virus will persist in patients with either previous infection or prior vaccination (32, 33).

Hepatitis B

The appearance of HBsAg predates clinical symptoms by 4 weeks on average and remains detectable for 1–6 weeks (Fig. 1). The chronic carrier state for HBV is defined by persistence of HBsAg and the absence of hepatitis B surface IgG antibody (anti-HBs), which is the protective antibody that defines immunity (Fig. 2). Titers of anti-HBs (in noncarriers) increase slowly during clin-

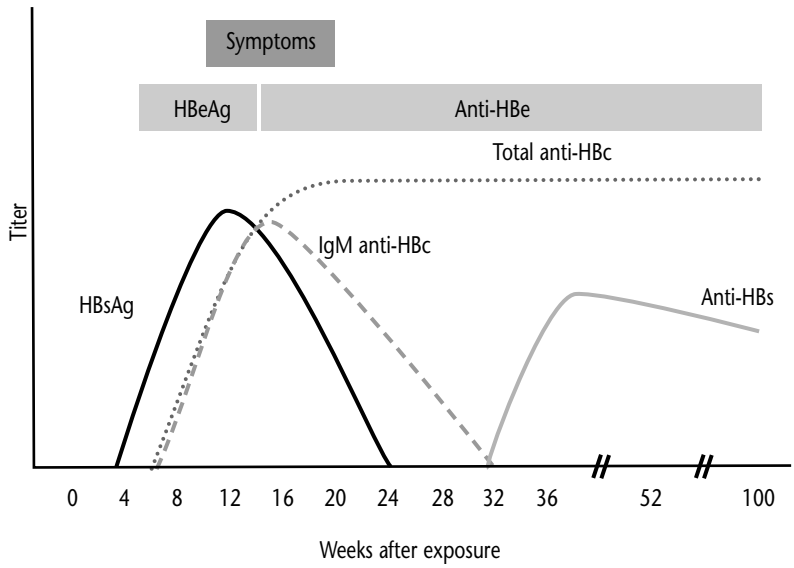

Figure 1. Typical serologic course of acute hepatitis B virus infection with recovery. (Centers for Disease Control and Prevention slide set adapted from Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices [ACIP] part II: immunization of adults. MMWR Recomm Rep 2006;55(RR-16):1–33; quiz CE1–4.)

ical recovery and continue to increase for up to 10–12 months after HBsAg has been cleared. In most patients with self-limited acute HBV infection, anti-HBs and HBsAg do not coexist detectably in serum, and anti-HBs is seen only after HBsAg has been cleared. The chronic carrier state usually can be predicted by HBsAg seropositivity for more than 20 weeks (8, 13, 32, 33).

A serologic "window" has been described for HBV infection when, despite clinical symptoms, HBsAg is clearing and undetectable but anti-HBs is not yet detectable either. In this period, HBV infection can still be diagnosed by detection of hepatitis B core IgG antibody (anti-HBc), which appears 3–5 weeks after HBsAg. Hepatitis B core IgG antibody is present only in the context of natural HBV infection and is not a protective antibody. It does not distinguish acute resolving infections from the chronic infection state, which is done only by persistence or clearance of HBsAg. An IgM antibody to the hepatitis B core antigen (IgM anti-HBc) appears during acute or after recent HBV infection and is present for approximately 6 months. In contrast, only anti-HBs becomes detectable in serum of vaccinated individuals. Therefore, the detection of anti-HBs in the absence of HBsAg and anti-HBc distinguishes vaccine-mediated immunity from natural infection-based immunity (where anti-HBc and anti-HBs are both present without HBsAg). Hepatitis B core antigen is not detectable outside of research laboratory assays, and tests for it should not be ordered as part of a "hepatitis B panel" (8, 13, 32, 33). With the variety of HBV-specific antigens and antibodies identified, interpretation of hepatitis B serologies is complex (Table 2).

Hepatitis C

The diagnosis of hepatitis C is confirmed by the identification of the antibody to hepatitis C virus, via a second- or third-generation enzyme immunoassay (ELISA) (34). The antibody may not be present until 6–10 weeks after the onset of clinical illness. Hepatitis C viral RNA can be detected by polymerase chain reaction assay of serum soon after infection, as well as in chronic disease. These other more specific tests for HCV, including HCV-specific RNA testing and genotyping, are available to define the specificity of infection, given that there are small but real false-positive rates associated with antibody testing or screening that vary with prevalence or risk of the disease in the screened populations. Such DNA-based specific testing usually is best interpreted by specialists trained in the treatment of hepatitis, to whom patients with positive serologic antibody test results should be referred (34). A reference table for the interpretation of these tests is available from the Centers for Disease Control and Prevention (Table 3).

Hepatitis D

Laboratory tests that may be used to confirm the diagnosis of acute hepatitis D are the detection of D antigen in hepatic tissue or serum and the identification of the IgM antibody to hepatitis D virus. Hepatitis D antigene-

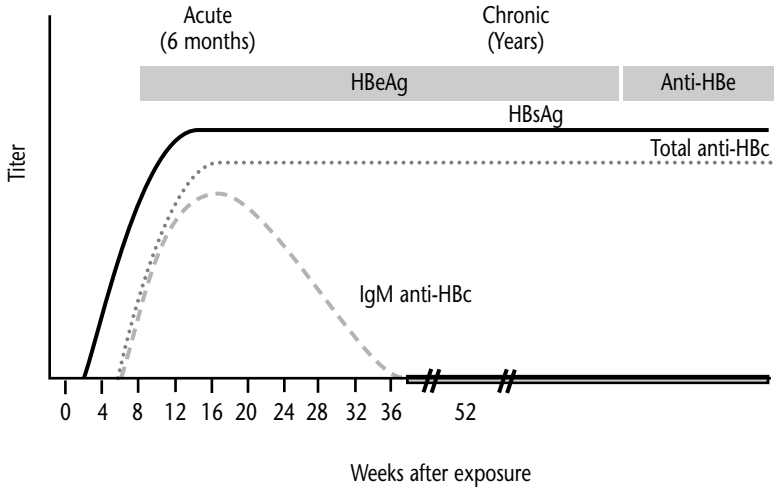

Figure 2. Progression to chronic hepatitis B virus infection: typical serologic course. (Centers for Disease Control and Prevention slide set adapted from Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults. MMWR Recomm Rep 2006;55(RR-16):1–33; quiz CE1-4.

Table 2. Interpretation of Hepatitis B Virus (HBV) Testing

Test	Results	Interpretation
HBsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination*
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Four interpretations possible†
Anti-HBc	Positive	
Anti-HBs	Negative	

*Antibody response (anti-HBs) can be measured quantitatively or qualitatively. A protective antibody response is reported quantitatively as 10 or more milli-international units (10 mIU/mL or less) or qualitatively as positive. Postvaccination testing should be completed 1–2 months after the third vaccine dose for results to be meaningful.

†Four interpretations:

Might be recovering from acute HBV infection

Might be distantly immune and test not sensitive enough to detect very low level of anti-HBs in serum

Might be susceptible with a false-positive anti-HBc

Might be undetectable level of HBsAg present in the serum and the person is actually chronically infected

Definitions

Hepatitis B surface antigen (HBsAg): A serologic marker on the surface of HBV. It can be detected in high levels in serum during acute or chronic hepatitis. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection.

Hepatitis B surface antibody (anti-HBs): The presence of anti-HBs generally is interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.

Total hepatitis B core antibody (anti-HBc): Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus (HBV) in an undefined time frame.

IgM antibody to hepatitis B core antigen (IgM anti-HBc): This antibody appears during acute or recent HBV infection and is present for approximately 6 months.

Centers for Disease Control and Prevention. Interpretation of the hepatitis B panel. Atlanta (GA): CDC; 2006. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/b/Bserology.htm. Retrieved July 11, 2007.

mia usually persists in patients with chronic hepatitis D despite the appearance of the IgG antibody to the virus. Thus, as in hepatitis C and HIV infection, viremia and end-organ damage can continue despite the presence of the antibody to the virus (35).

Hepatitis E

The diagnosis of infection with hepatitis E is documented by the presence of virus-specific antibodies in individuals with risk factors. The primary risk factor is travel exposure (33).

▶ *How are pregnant patients who are presumed chronic hepatitis carriers treated?*

Persons with diagnosed chronic HBV and HCV infection should be referred for evaluation to a physician experienced in the management of chronic liver disease. Diagnosis in the context of pregnancy-specific screening opens the opportunity for individuals who might otherwise have not ever been tested to receive appropriate subspecialty care for counseling and targeted treatment, usually after delivery. Women who are chronic carriers of HBV or HCV should inform sexual, household, and

Table 3. Interpretation of Hepatitis C Virus (HCV) Test Results

If HCV Test Result Is:			Interpretation		Action
Anti-HCV Screening Test Result*	Anti-HCV Supplemental Test Result				
	RIBA†	HCV RNA	Anti-HCV Result	HCV Infection	Additional Testing or Evaluation
Negative	Not needed	Not needed	Negative	None	No
Positive	Not done	Not done	Not known	Not known	Supplemental anti-HCV (RIBA) or HCV RNA
Positive	Not done	Negative	Not known	Not known†	Supplemental anti-HCV (RIBA)
Positive (high s/co ratios†‡)	Not done	Not done	Positive	Past/current	Evaluate for chronic infection and liver disease
Positive	Negative	Not needed	Negative	None	No
Positive	Positive	Not done	Positive	Past/current	Evaluate for chronic infection and liver disease
Positive	Positive	Negative	Positive	Past/current§	Repeat HCV RNA
Positive	Positive/not done	Positive	Positive	Current	Evaluate for chronic infection and liver disease
Positive	Indeterminate	Not done	Indeterminate	Not known	Test for HCV RNA or repeat anti-HCV testing
Positive	Indeterminate	Positive	Indeterminate	Current	Evaluate for chronic infection and liver disease
Positive	Indeterminate	Negative	Negative	None	No

*EIA, enzyme immunoassay or CIA, enhanced chemiluminescence immunoassay

†Recombinant immunoblot assay, a more specific anti-HCV assay viremia.

‡Samples with high signal-to-cutoff (s/co) ratios usually more than 95%) confirm positive, but supplemental serologic testing was not performed. Less than 5 of every 100 test results might represent false-positives; more specific testing should be requested, if indicated.

§Single negative HCV RNA result cannot determine infection status; patients might have intermittent viremia.

Centers for Disease Control and Prevention. Reference for interpretation of HCV test results. Atlanta (GA): CDC; 2006. Available at: http://www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/hcv_graph.pdf. Retrieved July 11, 2007.

needle-sharing contacts of their status and learn about and use methods to prevent or reduce the risk of transmission of infections to others. All HBsAg-positive laboratory results should be reported to the state or local health department in accordance with state requirements for reporting of chronic HBV infection (8, 13).

▶ *How can the risk of vertical transmission of HBV be reduced?*

Because hepatitis B virus is highly pathogenic and infectious, perinatal transmission of infection represents the single largest cause of chronically infected individuals worldwide. Because risk-factor-based prenatal screening protocols have been shown to detect at most 60% of women who are HBV carriers, routine prenatal screening of all pregnant women with HBsAg is recommended (13). Approximately 10–20% of women who are seropositive for HBsAg alone transmit the virus to their neonates in the absence of neonatal immunoprophylaxis. In women who are seropositive for both HBsAg and HBeAg, the frequency of vertical transmission increases to approximately 90% without neonatal prophylaxis. For adult-acquired HBV infection, the risk of chronic infection and its sequelae is only 5–10%. In contrast, HBV infection acquired perinatally carries an 85–95% risk of persistence and chronic infection, with a 25–30% lifetime risk of serious or fatal liver disease.

In patients with acute hepatitis B, the frequency of vertical transmission also depends on the time during gestation that maternal infection occurs. When it occurs in the first trimester, up to 10% of neonates will be seropositive for HBsAg. In women acutely infected in the third trimester, 80–90% of offspring will be infected (13).

The Centers for Disease Control and Prevention recommends universal active immunization of all infants born in the United States. The immunization schedule for infants of women who have been screened and have negative results should be started preferably before discharge, but by no later than 2 months of age. Preterm infants weighing less than 2,000 g and born to women who are HBsAg negative should have their first vaccine dose delayed until 1 month after birth or hospital discharge (13).

Current guidelines stipulate that infants of women who are HBsAg positive or whose status is unknown at the time of delivery also should receive both HBIG and hepatitis B vaccine within 12 hours of birth given simultaneously at different sites intramuscularly. It should then be followed by two more injections of hepatitis B vaccine in the first 6 months of life. The physician responsible for the care of a newborn delivered of a woman with chronic hepatitis B should be informed of her carrier status so that the appropriate doses of hepatitis B vaccine and HBIG can be given as soon as possible after delivery (13).

Neonatal immunoprophylaxis will not prevent HBV infection in newborns who are already infected in utero; therefore, current research is focusing on the potential efficacy of antepartum treatment of HBV-infected women to lower the risk of such infection, particularly in women who have risk factors for transmission (36–39). In addition, women who did not receive prenatal care will have unknown HBV status at the time of delivery, and these women have been shown to have significantly higher rates of being chronic HBV carriers than women enrolled in prenatal care (40). The combination of passive and active immunization has been particularly effective (85–95% efficacy) in reducing the frequency of perinatal transmission of hepatitis B virus.

▶ *How can transmission of other forms of hepatitis be prevented?*

Hepatitis C virus seroprevalence rates of 0.6–6.6% have been reported in study cohorts of pregnant women worldwide (41–44). Vertical HCV transmission rates of 2–8% have been demonstrated, with maternal viremia (detectable presence of HCV RNA in blood) an almost uniform prerequisite for transmission (35, 45–47). In pregnancies among HCV-infected mothers who were HCV RNA negative, vertical transmission was rare. Maternal coinfection with HIV significantly increases the risk of vertical HCV transmission to as much as 44% (45, 47). In a recent cohort study, risk factors associated with an increased rate of vertical HCV transmission to include higher maternal HCV viral titer, prolonged membrane rupture during labor (6 hours or longer), and use of internal fetal monitoring during labor were reported (48). If duration of membrane rupture and internal fetal monitoring are confirmed to be associated with transmission in further investigations, interventions may be possible to decrease the risk of transmission.

Currently, no preventive measures are available to lower the risk of vertical HCV infection of neonates as there are for HBV. Routine prenatal HCV screening is not recommended; however, women with significant risk factors for infection (see the box) should be offered antibody screening. Testing for HCV RNA should not be used for screening purposes.

Vertical transmission of hepatitis D virus has been documented. Transmission is uncommon, however,

Risk Factors Warranting Hepatitis C Screening: CDC Guidelines

Individuals who should be screened routinely:

1. Persons who ever injected illegal drugs (even once)
2. Persons notified that they received blood products before 1987 or from a donor who later tested positive for hepatitis C virus (HCV)
3. Recipients of transfusions or organ transplants, particularly if received before July 1992
4. Persons ever on long-term hemodialysis
5. Persons with persistently elevated alanine aminotransferase (ALT) or other evidence of liver disease
6. Persons seeking evaluation or care for a sexually transmitted infection, including human immunodeficiency virus

Individuals for whom routine testing is of uncertain need:

1. Recipients of tissue transplants (eg, cornea, skin, sperm, ova)
2. Users of intranasal cocaine or other illegal noninjected drugs
3. Persons with a history of tattooing or body piercing
4. Persons with a history of sexually transmitted diseases or multiple sexual partners
5. Long-term steady sex partner of an HCV-infected individual

Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR 1998;47(RR-19):1–33 and Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. MMWR 2006;55(RR-11):1–94.

because the measures used to prevent perinatal infection with hepatitis B virus are almost uniformly effective in preventing infection by hepatitis D. Vertical transmission of HEV has been reported, but information is limited.

▶ *Are there special considerations for intrapartum care in the context of maternal hepatitis infection?*

Between 85% and 95% of cases of perinatal transmission of HBV occur as a consequence of intrapartum exposure of the infant to infected blood and genital tract secretions. The remaining cases result from hematogenous transplacental dissemination and close postnatal contact between the infant and the infected parent. Risk factors for intrauterine HBV infection have been reported to include maternal HBeAg seropositivity, history of threatened preterm labor, higher HBsAg and HBV DNA titers, and the presence of HBV DNA in villous capillary endothelial cells (49). Adequate data regarding the risk of transmission with operative vaginal delivery or internal fetal monitoring are not available to make recommendations.

The route of delivery has not been shown to influence the risk of vertical HCV transmission (35, 50). Cesarean delivery should be performed in HCV-infected women only for obstetric indications.

▶ *What is the safety of invasive prenatal diagnostic procedures for patients with chronic hepatitis?*

The risk of transmission through amniocentesis appears to be low for women who are chronically infected with hepatitis B or hepatitis C, although the number of exposed cases in the literature is small. Of the 115 women reported to be positive for hepatitis B surface-antigen who underwent second-trimester amniocentesis, the rate of neonatal infection was no different than in women who did not have an amniocentesis. All of the infants received hepatitis B vaccination and immunoprophylaxis beginning at birth (50–53). There is only one series of 22 HCV-positive women reported in the literature who underwent second-trimester amniocentesis. No infants in this series were found to be hepatitis C RNA positive on postnatal testing. This group included one woman with hepatitis C RNA-positive amniotic fluid (54). Data are insufficient in the literature to assess the risk of chorionic villus sampling in these women or to estimate the risk of fetal infection among women with anterior placentas, those who are HBe antigen positive, or those with high hepatitis B or hepatitis C viral loads.

Because of the limited information regarding the risk of invasive procedures in women chronically infected with hepatitis B or hepatitis C, it would be prudent to discuss noninvasive screening options with these women.

▶ *Is breastfeeding contraindicated for infants of women with hepatitis?*

In HAV-infected women, breastfeeding is permissible with appropriate hygienic precautions. Although immune globulin has been administered to newborns in specific situations, the efficacy of this practice has not been established. Breastfeeding is not contraindicated for women who are HBsAg positive at the time of delivery. In addition, breastfeeding is not contraindicated in women chronically infected with HBV if the infant receives HBIG passive prophylaxis and vaccine active prophylaxis (13). There are no data from which to make a recommendation for HBeAg positive patients. In addition, breastfeeding has not been associated with an increased risk of neonatal HCV infection (56–59) and, therefore, is not contraindicated in HCV-infected mothers (58, 59).

Breastfeeding was not detrimental to newborns of HEV-infected women in one recent series of 93 pregnancies. In this cohort, anti-HEV antibody and HEV RNA were present in clostral samples, but at significantly lower levels than in maternal serum (60).

Immunotherapy

▶ *What is the role of specific immunotherapy in the treatment of chronic hepatitis in pregnancy?*

Hepatitis A

Given the nonchronic and usually self-limited course of symptomatic HAV infection, no specific antiviral agent is used for its treatment. The hepatitis A vaccine is not contraindicated during pregnancy. In populations that have expected high rates of previous HAV infection, prevaccination testing may be considered to reduce costs by not vaccinating persons who are already immune. Prevaccination serologic testing may be cost-effective for adults who were born in or lived for extended periods in HAV-endemic areas; adults in certain population groups (Native Americans, Alaska Natives, and Hispanics); and adults in groups with a high prevalence of infection (eg, injection drug users) (25).

Patients who have had close personal or sexual contact with an HAV-infected individual should receive

postexposure prophylaxis if they have not been immunized. Immune globulin does not pose a risk to either a pregnant woman or her fetus and should be administered during pregnancy if indicated. Immune globulin provides protection through passive antibody transfer. For postexposure prophylaxis, a single intramuscular dose of 0.02 mL/kg should be administered as soon as possible after contact with the infected individual; this confers protection for up to 3 months at an 80–90% efficacy level. Administration of immune globulin more than 2 weeks after exposure is not effective in preventing or ameliorating the severity of hepatitis A (25). The HAV vaccination series also should be initiated in conjunction with postexposure administration of IgG. Although some studies suggest that HAV vaccine alone also may prevent postexposure infection, no comparative trials have been conducted (29). This strategy of administering HAV vaccine alone for postexposure prophylaxis in individuals younger than 40 years has been proposed by some experts.

Hepatitis B

No specific therapy is available for treatment of acute HBV infection. Persons with chronic HBV infection should be referred for evaluation to a physician experienced in the management of chronic liver disease.

Therapeutic agents have been approved by the FDA for treatment of chronic HBV infection and can achieve sustained suppression of HBV replication and remission of liver disease in some persons (32). One of these agents, the antiviral agent lamivudine, also has been shown to be effective, in combination with other medications, for both the treatment of infections with the human immunodeficiency virus (HIV) and for the interruption of vertical HIV transmission. Recent research has demonstrated potential benefit from lamivudine treatment in decreasing the risk of in utero HBV infection in women who were HBV carriers during the last months of pregnancy (37, 39). Other investigators have studied the use of hepatitis B immune globulin (HBIG) administered to the mother toward the end of pregnancy to achieve similar results (36, 38).

Hepatitis C

Optimal obstetric care of women infected with HCV is limited by the lack of any available prenatal or postnatal pharmacologic or immunologic measures to decrease the risk of vertical transmission. Use of antiretroviral treatment to decrease both maternal viral titers and the risk of neonatal HIV infections (61) raises the question of the potential for comparable treatment of maternal HCV infection, given that maternal HCV titer also has been associated with an increased risk of transmission (44, 46). Recent advances in combination therapy for HCV infection in nonpregnant adults have made sustained normalization of transaminase levels and clearance of HCV RNA possible, even in individuals with HCV genotypes that have a poorer prognosis (62). More recently, the modification of interferon alfa-2a via a branched-chain polyethylene glycol moiety has produced a compound, peginterferon alfa-2a, with prolonged absorption, slower clearance, and a longer half-life than standard interferon, allowing once-weekly dosing (63). Randomized trials have shown peginterferon to be superior to standard interferon, either alone or in combination with ribavirin, for the treatment of chronic HCV infection in adults (64). Even though the use of ribavirin is contraindicated in pregnancy, interferon has been used safely for the treatment of T-cell leukemias during pregnancy (65, 66), and its potential role as an anti-HCV therapy for both maternal benefit and fetal and neonatal benefit warrants further study.

▶ *How can accidental or occupational exposures to hepatitis virus be managed?*

Accidental exposures are classified as occupational or nonoccupational for management recommendations. Guidelines for postexposure prophylaxis of occupational exposures have been published by the Centers for Disease Control and Prevention (13, 67, 68) and are intended for use in settings in which postvaccination testing is recommended for certain employees and in which programs are available to implement testing and follow-up algorithms. There are also specific guidelines for care of persons with nonoccupational exposure to HBV through exposure to blood or body fluids (13).

All health care workers who may be exposed to blood or blood products should be vaccinated against hepatitis B. The principal mechanism of transmission of HBV from patient to health care workers is through injury from a sharp object that is contaminated with infected blood. Of all the bloodborne transmissible viruses (including HCV and HIV), HBV exists in highest concentrations in blood. Hepatitis B requires much smaller volumes for transmission and, therefore, can be injected without hollow-bore needles or deep penetrating injuries. The risk of infection per injury with HBV-infected blood is 20–30%. Transmission of HBV also has been reported by mucosal contamination from body fluid "splash" exposures.

The risk of health care workers acquiring HCV infection through workplace exposure to infected blood is lower than the risk of acquiring HBV (30%) and high-

er than the risk of acquiring HIV (0.3%) (68, 69). Standard precautions such as not recapping used needles has been shown to decrease the risk of workplace injury; however, recent research has demonstrated that even practitioners in high-risk subspecialties failed to routinely practice standard universal precautions (69).

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- Routine prenatal screening of all pregnant women by HBsAg testing is recommended.
- Newborns born to hepatitis B carriers should receive combined immunoprophylaxis consisting of HBIG and hepatitis B vaccine within 12 hours of birth.
- Hepatitis B infection is a preventable disease, and all at-risk individuals, particularly health care workers, should be vaccinated. All infants should receive the hepatitis B vaccine series as part of the recommended childhood immunization schedule.
- Breastfeeding is not contraindicated in women with HAV infection with appropriate hygienic precautions, in those chronically infected with hepatitis B if the infant receives HBIG passive prophylaxis and vaccine active prophylaxis, or in women with HCV infection.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Routine prenatal HCV screening is not recommended; however, women with significant risk factors for infection should be offered antibody screening.
- Route of delivery has not been shown to influence the risk of vertical HCV transmission, and cesarean delivery should be reserved for obstetric indications in women with HCV infection.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- The risk of transmission of hepatitis B associated with amniocentesis is low.
- Susceptible pregnant women who are at risk for hepatitis B infections should be specifically targeted for vaccination.

Proposed Performance Measure

Percentage of women receiving prenatal care who are screened for hepatitis B by hepatitis B surface antigen testing

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and February 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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