HEPATITIS IN PREGNANCY — A REVIEW

CHANTEL IMRAN AND LESLIE M HANSEN
Department of Gynecology and Obstetrics,
Jefferson Medical College, Thomas Jefferson
University, and Pennsylvania Hospital.

INTRODUCTION

Liver disease is a relatively common complication of pregnancy and includes disease such as pre-eclampsia, the help (hemolysis, elevated liver function tests, low platelets) syndrome, acute fatty liver, and cholestasis of pregnancy. However, the most common cause of jaundice and serious liver disease during pregnancy is viral hepatitis. In the United States (U.S.), approximately 1-3% of all pregnancies will be affected by one of the hepatitis serotypes. Recently, the CDC adopted guidelines for hepatitis screening during pregnancy Table-I. This preventative health measure hopefully will minimize the adverse effects of hepatitis during pregnancy. In this article, each of the hepatitis viruses will be reviewed with emphasis on their effects on pregnancy, transmission rates, and risk factors for acquiring these diseases.

Hepatitis-A

The hepatitis A virus (HAV) is a 27 nm single stranded RNA enterovirus of the picornavirus group, most commonly transmitted through the fecal oral route or by contaminated food or water. Risk factors for transmission include poor sanitation, crowded living conditions, working in daycare center, international travel, homosexual activity, and IV drug use.

Acute infection occurs with an annual incidence of 23 per 100,000 in the U.S. with primary symptoms of fever, malaise, and anorexia after an average incubation period of 30 days. HAV infection represents 26-28% of all acute hepatitis cases reported to the CDC. Approximately 40% of the U.S. population is anti-HAV positive, representing prior infection which may have been asymptomatic in the acute presentation. Hepatitis A is self-limited, does not result in chronic disease or carrier state and infection usually provides lifelong immunity.

Risk factors, transmission, and the clinical course of hepatitis A in the pregnant patient is no different from the nonpregnant patient. Patients usually recover from acute hepatitis A infection in 4-6 weeks. Only mothers with active HAV are at risk to transmit this infection to their infant. Transplacental infection is extremely uncommon. Mothers with acute hepatitis A most often transmit the disease to their infant during the neonatal period from fecal exposure. In contrast to adults, hepatitis A in infants is rarely clinically apparent.

HAV infection is diagnosed by measurement of anti-HAV infected pregnant patients is supportive and includes a diet with adequate protein and instructions to limit drugs that depend on hepatic metabolism. The current recommendation for post-exposure prophylaxis of acute HAV infec-
tion is 0.02 ml/kg IM of immune serum globulin within 2 weeks of exposure. This recommended dose for pregnant and non-pregnant patients is about 85% effective in preventing active hepatitis. Neonates born to acutely HAV infected mothers may also be candidates for this immunoprophylaxis. An inactivated vaccine has recently been developed and is currently licensed in many countries, although FDA approval in the US is still pending.3

**Hepatitis-B**

Hepatitis B virus (HBV) is a double stranded circular 42 nm DNA hepadna virus found in blood, saliva, genital secretions, cerebrospinal fluid, ascites, breast milk, synovial fluid, and urine. Hepatitis B infection usually follows an acute self limited course. There is a 70-80 day incubation period followed by complete recovery and resultant lifelong immunity in most cases. Acute infection may cause fulminant hepatitis with massive liver cell necrosis and hepatic failure occurring in 1% of those infected. HBV infection may also result in a chronic carrier state with the long term risk of developing hepatocellular carcinoma. The prevalence in the U.S. of HBV is less than 1%, however, there are 200 million chronic carriers of HBV worldwide. In the U.S., women at greatest risk for HBV infection are Asian, Haitian, African, Eastern European, Middle Eastern, and Native Alaskan (15%), those with occupational exposure (0.5-1.0%), women in institutions (3%), those with chronic liver disease, illicit drug users, a history of blood product transfusion (7-10%), and women in households with other HBV infected individuals (6-13%).4

The worldwide prevalence of HBV infection during pregnancy is 1-2/1,000 for acute infection and 5-15/1,000 for the chronic carrier state.5 Perinatal transmission of hepatitis B virus occurs primarily from exposure to blood and genital secretions during delivery, although in utero transmission may occur. There is no evidence that cesarean section lowers the risk of HBV transmission.

**TABLE - I**

The CDC recommends that all pregnant women be tested for hepatitis B as part of routine prenatal care.

HbsAg testing should be done early in pregnancy with other prenatal screening tests.

All infants should receive the HBV recombinant vaccine at birth, one month and six month of age.

Infants born to HBsAg positive mothers should also receive HBV immune globulin within the first week. The greatest efficacy occurs when the vaccine is given within the first 12 hours of life.

If a woman tests HbsAg positive, her liver enzyme should be checked and household contacts should also be tested and vaccinated, if indicated.

Vertical transmission of HBV is more common if acute infection of the mother occurs during the third trimester or in the postpartum period. Risk of transmission also correlates with the maternal viral load at the time of delivery, with transmission being more likely with high titers of hepatitis B surface antigen (HBsAg) and hepatitis B antigen (HBeAg). Transmission of HBV in women infected during the first trimester rarely occurs.6,7 The vertical transmission rate with acute infection during the second trimester is reported to be 6-25% and 67-70% during the third trimester.6,7 Vertical transmission occurs in 90% of cases if the mother is both HBsAg positive and HBeAg positive. Those who are acutely infected and are HBsAg positive and HBeAg negative have only a 10-20% transmission rate.8 Infants who are HBeAg positive typically develop a much more severe and fulminant neonatal course if transmission occurs. There has been no report of a teratogenic syndrome related to the presence of maternal HbsAg or maternal disease, although HBV may be associated with preterm contractions and uteroplacental insufficiency. The risk of neonatal HBV infection in infants born to
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chronic carrier mothers is 5-15% if neonatal vaccination is administered. Transplacental transmission of HBV is greater if the mother is acutely affected during pregnancy than if the mother is a chronic carrier.9

The current CDC recommendation for hepatitis B screening is serologic evaluation for HBsAg of all mothers at the first prenatal visit. This screening has been shown to be cost effective, especially for prevention of hepatitis B infection in infants of affected mothers and the long term prevention of chronic carriers and fulminant liver disease.10 If hepatitis is suspected or the mother is at a high risk for HBV exposure, a second HBsAg test should be considered later in the pregnancy. If the mother is HBsAg positive, hepatitis B immune globulin 0.06 mL/kg IM and HBV recombinant vaccine should be given to the infant within 12 hours of birth. The vaccine should again be administered at one and six months of age. If the mother is HBsAg negative, the vaccine should be administered in the usual three dose course. If no prenatal HbsAg result is obtainable at the time of delivery, the mother should be assumed to be HBsAg positive and the above algorithm should be followed. This combination of vaccine and immune globulin has been shown to 85-95% effective in preventing neonatal HBV infection. In utero infection of HBV, however, is not preventable by prophylaxis begun at birth.

Most women with hepatitis B infection during pregnancy can be managed on an outpatient basis. Supportive measures such as bed rest and a high protein, low fat diet should be encouraged. Hospitalization is advised if severe anemia, diabetes, protracted nausea and vomiting, abnormalities in prothrombin time, bilirubin greater than 15 mg/dL, or severe edema complicate HBV infection tests, specifically AST (aspartate transaminase), ALT (alanine trans-
aminase) and bilirubin. These tests do not need to be repeated during the pregnancy unless clinical signs of liver failure such as jaundice, unexplained edema, or encephalopathy develop. Patients who are HBsAg positive should also be offered HIV testing.

Vertical transmission of HBV can occur through breast feeding, although there appears to be little risk for infants who have been given appropriate immunoprophylaxis. Therefore, current recommendations for HbsAg positive mothers are to allow breast feeding for infants who have received HBV immune globulin and the HBV vaccine.

If neonatal HBV infection occurs, it is usually asymptomatic. However, 90% of acutely infected infants become chronic carriers, in contrast to fewer than 10% of adults. In contrast to adults, infants who develop chronic HBV infection are at high risk of developing hepatocellular carcinoma or cirrhosis and have a 25% mortality rate. Therefore, it is important to notify the pediatrician of the mother’s HBV status to allow adequate follow up of the infant. HBsAg and anti HBSAg testing at 12-15 months is recommended.

Hepatitis-C

The hepatitis C virus (HCV) is a 30-60 mm single stranded RNA virus similar to the flavivirus group that is responsible for more than 90% of post transfusion hepatitis cases. Other risk factors include IV drug use, multiple sexual partners, tattooing, and a history of organ transplantation. Clinical symptoms include malaise, fever, abdominal pain and jaundice usually after a 45-55 day incubation period, although 75% of acute infections with HCV are asymptomatic. Approximately 50% of acute infections progress to chronic liver disease defined as persistence of elevated alanine transaminase for more than six months.

The prevalence of HCV in the pregnant population is reported to be as high as 2.3%. The prevalence is 0.5-1.5% in blood donors. Chronic active hepatitis C in the pregnant patient increases the risk of prematurity and intrauterine growth retardation (IUGR). Acute hepatitis C infection does not usually have any adverse effects on pregnancy outcome. Pregnancy rarely alters the clinical course of acute hepatitis C infection.

Prenatal screening in the asymptomatic patient or in those not at risk for HCV infection is not currently recommended. However, testing for those at risk and those with jaundice or hepatitis of unknown etiology involves detection of anti HCV antibody by Elisa with anti HCV recombinant immunoblot assay to confirm a positive result.

In utero transmission of HCV varies according to trimester and acuteness or chronicity of the mother’s HCV status. Transmission of HCV from mother to fetus occurs in as much as 87% of acutely infected women during the third trimester. As with hepatitis B, there is a minimal risk of transmission in the first and second trimesters. Third trimester transmission during acute maternal disease most likely occurs at delivery rather than in utero, although the circumstances and risk factors are not yet clear. In contrast, mothers with chronic HCV have a risk of direct transplacental maternal fetal transmission of HCV shown to be as high as 85%. Neonatal transmission of HCV through breast feeding. Only 25% of infants with serologic HCV infection are clinically symptomatic. Approximately half of HCV infected infants develop chronic HCV infection, with 20% of these carriers eventually developing hepatocellular carcinoma, the leading cause of cancer death in the world.

Immune serum globulin is available with a recommended dose of 0.06 ml/kg for
those with percutaneous exposure to a person with potential or established HCV infection. However, the value of this regimen is currently uncertain with studies show in variable efficacy. To our knowledge, using immune globulin to prevent vertical transmission from HCV positive mothers has not been studied and currently no vaccine for HCV is available.

**Hepatitis-D**

The hepatitis D virus (HDV) is a 36 nm single stranded RNA viroid or satellite virus consisting of a circular RNA core with an outer coat of HBsAg. HDV infection occurs exclusively in conjunction with HBV infection, as HDV is considered a defective virus that cannot assemble itself without the presence of HBsAg. Risk factors for HDV are similar to those for HBV infection and approximately 20-25% of chronic HBV patients will eventually become superinfected with HDV.

Diagnostic tests for HDV include Elisa for anti HDV antibody, both IgM and IgG forms, which are identifiable in serum and hepatic tissue. Immunofluorescent staining of hepatic tissue obtained by biopsy is being performed in research laboratories, but is not yet widely available. Screening for HDV may be done for those who are found to be HBV positive.

Vertical and perinatal transmission of HDV has been reported, but is fortunately, uncommon because HBV immunoprophylaxis is effective in preventing HDV infection. There is no immunotherapy available for prevention or cure of HDV. Currently, vaccination and immune globulin against hepatitis B for those at risk is the best prevention for HDV infection.

**Hepatitis-E**

Hepatitis E virus (HEV) is a 32 nm single stranded RNA virus related to the calicivirus group transmitted by the fecal oral route. Hepatitis E is rare in the U.S., being most common in areas of the world with poor sanitation, especially following floods. Endemic areas are reported in many Asian and African countries, the former Soviet Union, and in Mexico. HEV is rare in the U.S. with sporadic cases occurring in travelers returning from endemic areas.

Symptoms usually mimic the typical course of gastroenteritis and other types of hepatitis with no chronic carrier state following recovery. There is a worse prognosis in the malnourished and medically undeserved. Western blot studies for detection of HEV infection have been developed, although they are not available for routine clinical testing.

Pregnant patients are more susceptible to HEV exposure and have more serious sequelae from the disease than nonpregnant patients. The pregnant patient is especially susceptible to hepatitis E infection in epidemic areas with an infectivity rate of 17.3% in pregnant women compared to 2.1% in nonpregnant women. A 20% maternal mortality rate is reported in pregnant patients who develop HEV infection (especially in the third trimester), with higher rates of fulminant hepatitis and disseminated intravascular coagulation (DIC). If the mother survives the acute infection, there may still be an increased risk of fetal loss, including intrauterine and neonatal deaths. Pregnancy does not increase the risk of progression to fulminant disease and death in HEV infected patients.

Clinically, HEV illness is more symptomatic in adults than in children. Improved sanitation and supportive care for those infected seem to be the best treatments. Immune globulin is infective, as it does not contain sufficient antibodies to confer protection. Recombinant HEV vaccines, however, are currently under development.
CONCLUSION

Viral hepatitis is a common disease of pregnancy. In most studies, pregnancy has not been demonstrated to adversely affect the course of viral hepatitis. However, risks to the fetus or neonate are substantial and adequate chemoprophylaxis of exposed newborn is critical in preventing transmission of the disease. Advances in the therapy or viral hepatitis have had the most significant impact on neonatal morbidity and mortality. Immune globulin and vaccination has reduced the number of acute neonatal infection by over 90%. Screening for hepatitis B in pregnancy identifies those mother at risk for perinatal and neonatal transmission. This has been implemented to reduce the maternal neonatal transmission rate and prevent hepatitis from occurring in newborn of infected mothers.

REFERENCES