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Hepatitis B and C in pregnancy: a review and recommendations for care

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Abstract

Our objective was to provide a comprehensive review of the current knowledge regarding pregnancy and hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as well as recent efforts to reduce the rate of mother-to-child transmission (MTCT). Maternal infection with either HBV or HCV has been linked to adverse pregnancy and birth outcomes, including MTCT. MTCT for HBV has been reduced to approximately 5% overall in countries including the US that have instituted postpartum neonatal HBV vaccination and immunoprophylaxis with hepatitis B immune globulin. However, the rate of transmission of HBV to newborns is nearly 30% when maternal HBV levels are greater than 200 000 IU ml^{-1} (>6 $\log_{10}$ copies ml^{-1}). For these patients, new guidelines from the European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) indicate that, in addition to neonatal vaccination and immunoprophylaxis, treating with antiviral agents such as tenofovir disoproxil fumarate or telbivudine during pregnancy beginning at 32 weeks of gestation is safe and effective in preventing MTCT. In contrast to HBV, no therapeutic agents are yet available or recommended to further decrease the risk of MTCT of HCV, which remains 3 to 10%. HCV MTCT can be minimized by avoiding fetal scalp electrodes and birth trauma whenever possible. Young women with HCV should be referred for treatment post delivery, and neonates should be closely followed to rule out infection. New, better-tolerated treatment regimens for HCV are now available, which should improve outcomes for all infected individuals.

INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are acquired by contaminated blood product exposure, sexual activity or perinatal transmission. Although the prevalence of HBV is relatively low in the US (0.4%), with approximately one million Americans chronically infected by HBV,[1] it is more prevalent in East Asia (8%)[2] (China 2 to 18%, Taiwan 2 to

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CONFLICT OF INTEREST

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19% and Hong Kong 4 to 10%, depending on the region),[3] Southeast Asia (>6%)[2] (Indonesia 2 to 9%, Thailand 1 to 25% and India 1 to 66%, depending on the region)[3] and sub-Saharan Africa (8 to 12%).[2] Both Tropical Latin America and Central Latin America have had a decrease in HBV prevalence since 1990 (to 1.6% in 2005).[2] HCV is the most common chronic blood-borne infection in the US, affecting nearly four million Americans. Women of childbearing age have a 1 to 2% incidence of chronic HCV infection, with higher rates in those with risk factors such as intravenous drug use.[4] Pregnancy in patients with chronic HBV or HCV is associated with mother-to-child transmission (MTCT) and may be associated with increased maternal and fetal complications. In this review, we discuss the relationship between HBV/HCV infection and adverse pregnancy outcomes. Also included is a perspective on the current strategies to decrease the rate of MTCT. The published literature was searched through MEDLINE and ClinicalTrials using search terms hepatitis and pregnancy. The 107 studies cited represent the consensus regarding management of HBV and HCV in pregnancy.

Epidemiology of chronic hepatitis B and chronic hepatitis C in pregnancy

In a large population-based study from Florida involving nearly 1.7 million pregnant women, the prevalence of HBV was approximately 27 times higher among Asian-Americans and 5 times higher among African-Americans as compared with whites. Conversely, prevalence rates for HCV were highest among white women.[5] There is an increased incidence of HIV infection in pregnant women with chronic HBV or HCV infection.[5,6] Moreover, high-risk behaviors such as smoking, alcohol abuse and drug abuse are increased in pregnant women with HBV or HCV infection.[6]

Pregnancy outcomes associated with HBV or HCV infection

Several large population studies indicate that there is increased risk for preterm birth (odds ratio 1.4; 11.5% vs 7.9%, $P<0.001$), low birth weight (<2500 g) (odds ratio 1.39; 10.4% vs 7.8%, $P = 0.009$), premature rupture of membranes (8.9% vs 6.9%, $P = 0.026$), gestational diabetes (13.2% vs 8.8%, $P<0.02$) and congenital abnormalities (odds ratio 1.55; 7.2% vs 5.1%, $P = 0.01$) in pregnancies associated with maternal HBV or HCV infection (Table 1).[5–12] Maternal chronic HCV infection is also associated with cholestasis of pregnancy,[7,13,14] neonatal narcotic withdrawal syndrome[7] and neonatal intensive care unit admission.[5,7,12]

A confounding factor that limits interpretation of these studies is exposure to illicit drugs during the prenatal period, especially heroin, methadone and amphetamines,[5,7] which are independently associated with low birth weight, preterm birth, congenital anomalies and other adverse neonatal outcomes.[7,15] Two of the largest studies showing adverse outcomes associated with HBV or HCV included drug abuse, alcohol abuse and tobacco use in the multivariate statistical analyses.[5,7] Nonetheless, although pregnancies complicated by HBV or HCV are clearly associated with adverse maternal and fetal outcomes, it is not as evident if the etiology of these events are mediated by the viral infection, by other confounding factors, or by a combination of factors.

HEPATITIS B IN PREGNANCY

In the US, the prevalence of chronic HBV infection in pregnancy is 0.2 to 6%, with rates varying by race and ethnicity.[10,16] In a study of pregnant women from four urban US areas, Asian-American women had the highest prevalence of chronic HBV infection (6%), followed by blacks (1%), whites (0.6%) and Hispanics (0.14%).[16] Newborn infants acquiring HBV infection by perinatal transmission have a greater than 95% chance of becoming chronic HBV carriers.[17–19] Therefore, it is very important to institute maximally effective measures to prevent MTCT.

Diagnosis of chronic hepatitis B

Chronic HBV infection is diagnosed by the presence of hepatitis B surface antigen (HBsAg) in serum for longer than 6 months (Table 2 and Figure 1).[20] Hepatitis B e antigen (HBeAg) is a marker of active viral replication and infectivity. *Immune-tolerant* chronic HBV patients have normal serum aspartate transaminase (AST) and alanine transaminase (ALT) levels, but have very high HBV DNA levels (>10 million IU ml $^{-1}$; >6 × 7 $\log_{10}$ copies ml^{-1}); they typically are children, teenagers or young adults. *Inactive HBV carriers* are HBsAg-positive, HBeAg-negative, hepatitis B e antibody positive, with undetectable or low (<1000 IU ml $^{-1}$;<6 × 3 $\log_{10}$ copies ml $^{-1}$) HBV DNA levels and normal liver function tests. Patients with *chronic active HBV infection* have increased AST and ALT levels, may be positive for HBeAg and have HBV DNA levels over 20 000 IU ml^{-1} (>5 $\log_{10}$ copies ml^{-1}).

Screening for chronic HBV infection

The Centers for Disease Control (CDC) recommends that all pregnant women should be screened for the presence of HBsAg at diagnosis of pregnancy (Figure 2).[21] Repeat screening should be considered in HBsAg-negative women with risk factors for HBV infection (Asian, drug use, sexual exposure, incarceration, abnormal ALT) on admission for delivery.

HBsAg-positive patients should be checked for the presence of HBeAg, hepatitis B e antibody and for HBV DNA level. High HBV DNA levels and HBeAg-positivity are associated with increased risk for MTCT of HBV infection.[22] Neonates of all HBsAg-positive mothers should receive immunoprophylaxis treatment with hepatitis B immune globulin (HBIG) and HBV vaccine at delivery to decrease MTCT of HBV infection.[23]

Pregnancy is not a contraindication for vaccination to HBV.[24] Therefore, pregnant women who are not immune to HBV should be vaccinated, because premature delivery may be increased if acute hepatitis B is acquired in the last trimester and because MTCT occurs in over 60% of pregnancies associated with acute HBV infection at or near term.[24,25]

Impact of pregnancy on chronic HBV infection

Pregnancy is well tolerated by women with chronic hepatitis B infection.[26] HBV DNA levels may increase during pregnancy in association with a decrease in ALT levels, consistent with an HBV tolerance phase, followed by a post-partum decline in HBV DNA level that is associated with increased ALT levels and active hepatitis, consistent with a

post-partum reconstitution of the immune system. This post-partum HBV reactivation may be associated with HBeAg seroconversion (i.e., clearance of HBeAg, development of hepatitis B e antibody positivity, decline in HBV DNA levels and normalization of ALT level) in 12.5 to 17% of patients.[27–29]

Mother-to-child-transmission of HBV infection

It is estimated that 30 to 40% of chronic HBV infections in the US are a result of perinatal transmission or early childhood infection.[30] The most important risk factor for MTCT of HBV infection is a maternal level of HBV DNA>200 000 IU ml^{-1} (>6 log_{10} copies ml^{-1}).[22,31–35] Prior to neonatal prophylaxis with HBIG and HBV vaccination (see detailed description in the following section), the risk of perinatal transmission of HBV infection ranged from 10 to 40%, with 40 to 70% of those infants remaining chronically infected.[36] The risk of MTCT was more than 90% when mothers had high HBV DNA levels and were HBeAg-positive (indicative of active viral replication and infectivity), and almost all of these infected infants became chronic HBsAg carriers.[17–19] Young women in the immune-tolerant phase of chronic HBV infection are at high risk (up to 30%) for MTCT of HBV infection, regardless of neonatal immunoprophylaxis with HBIG and HBV vaccine.[22,31,33,34,37,38] In contrast, chronic HBV infection occurred in fewer than 10% of infants of HBeAg-negative mothers.[39] Other risk factors for MTCT of HBV include threatened preterm labor, prolonged labor and prior failure of immunoprophylaxis in siblings.[31]

MTCT of HBV can occur at three stages of pregnancy: intrauterine, intra-partum or post-partum. MTCT of HBV infection is thought to occur predominantly at or after birth based on the high protective efficacy of immunoprophylaxis. Intrauterine MTCT of HBV is reported to occur in 10 to 16% of pregnancies and probably accounts for the small percentage of infants who do not respond to immunoprophylaxis treatment for HBV at birth.[40–42] Intrauterine transplacental transmission due to leakage of maternal blood can occur during threatened abortion.[43,44] The risk of transmission of HBV from amniocentesis is low; in one study, the rate of MTCT did not significantly differ between women with HBV who underwent amniocentesis from those who did not undergo amniocentesis (9 vs 11%).[45] The effect of other invasive procedures during pregnancy (chorionic villus sampling, cordocentesis, fetal surgery) on the risk of HBV transmission is unknown. No association between forceps or vacuum extraction during delivery and risk of HBV transmission has been demonstrated.[46]

Prevention of MTCT of HBV infection

Successes and failures of immunoprophylaxis: HBIG and HBV vaccination at birth—Current standard of care for the prevention of MTCT of HBV infection is treatment of the newborn with HBIG and HBV vaccination (Table 3). At-risk neonates who received HBV vaccine alone at birth had a 26 to 36% chance of MTCT of HBV infection,[47] whereas administration of HBIG alone at birth decreased the rate of perinatal HBV transmission to 15 to 20%.[23] If HBIG and the HBV vaccine are administered to the neonate of an HBsAg-positive mother within 12 h of delivery, approximately 5% of infants become chronic HBV

carriers, a reduction in MTCT of almost 90%.[47,48] Overall, the use of HBIG and HBV vaccine has reduced MTCT to 5 to 10%.[31,47,49,50]

The Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) recommend administration of HBV vaccine and HBIG to at-risk infants within 12 h of delivery, followed by completion of the hepatitis B vaccine series within the first year of life.[23] Newborns of mothers with unknown HBsAg status at the time of birth should receive the HBV vaccine within 12 h of birth; if the mother is found to be HBsAg-positive, the infant should receive HBIG as soon as possible (within 7 days of birth).

The 5% of children who develop chronic hepatitis B infection despite immunoprophylaxis either fail to receive the full regimen of HBV vaccination, fail to develop hepatitis B surface antibody (HBsAb) or are born to mothers with very high levels of HBV DNA (>200 000 IU ml $^{-1}$ or 6 $\log_{10}$ copies ml^{-1})[22] or who are HBeAg-positive.[50] Despite immunoprophylaxis, HBV is still transmitted from 8 to 30% of mothers with high levels of HBV DNA and HBeAg positivity.[31,33,37,38] For example, a recent Chinese study demonstrated a dose-dependent correlation between maternal pre-delivery HBV DNA levels and rate of immunoprophylaxis failure.[35] All infants who failed immunoprophylaxis were born to HBeAg-positive mothers with HBV DNA levels ≥6 $\log_{10}$ copies ml $^{-1}$ (≥ 200 000 IU ml $^{-1}$). In a meta-analysis from the Netherlands, the only factor that significantly affected the efficacy of immunoprophylaxis was the maternal HBV DNA level. There was 100% efficacy with HBV DNA less than 150 pg ml $^{-1}$ (~10^7 IU ml $^{-1}$; 6 × 7 $\log_{10}$ copies ml $^{-1}$), but only 68% efficacy with HBV DNA levels greater than 150 pg ml^{-1},[22] which is consistent with another report that found a 25 to 50% rate of MTCT of HBV infection with maternal HBV DNA levels over 150 pg ml $^{-1}$.[51] Finally, in an Iranian study of infants who received HBIG and HBV vaccine at birth, the rate of HBV infection was 1.5% in infants born to women who were HBeAg-negative and 18% for infants born to women who were HBeAg-positive.[50] HBV DNA levels were not analyzed.

Antiviral therapy for HBV in pregnancy—The significant rate of immunoprophylaxis failure in neonates of women with high HBV DNA levels led to the suggestion that antiviral therapy during the last trimester of pregnancy could decrease MTCT by reducing the level of HBV DNA at the time of delivery. To date, several antivirals have been examined, all of which are nucleos(t)ide analogues. In this section, we summarize those data.

Lamivudine, a cytosine analogue that acts as a nucleoside HBV reverse transcriptase inhibitor and thus is a potent replication inhibitor, produces a median 97% reduction in HBV DNA levels after 2 weeks.[52] Multiple randomized controlled trials[34,53,54] and two meta-analyses[54,55] have demonstrated that lamivudine therapy significantly decreases the likelihood of MTCT of HBV infection and is safe for the mother and newborn. The most recent meta-analysis included 15 randomized controlled trials with 1693 HBV carrier mothers and demonstrated that lamivudine treatment beginning at week 28 of pregnancy significantly decreased MTCT of HBV infection (relative risk 0.33 to 0.43); efficacy was dependent on a decrease in maternal HBV DNA levels to less than 6 $\log_{10}$ copies ml $^{-1}$ (200 000 IU ml^{-1}).[56] A randomized controlled Chinese trial with lamivudine 100 mg per day in HBeAg-positive mothers with HBV DNA greater than 6 $\log_{10}$ copies ml $^{-1}$ in the third

trimester of pregnancy demonstrated a significant reduction in immunoprophylaxis failure (18 vs 39%).[34] Starting lamivudine therapy at week 32 of pregnancy has been suggested to achieve a sufficient reduction in HBV DNA level in case of an early delivery.[31]

Although lamivudine is a pregnancy category C medication (based on studies in animals showing an adverse effect on the fetus), there are insufficient well-controlled studies in humans. However, potential benefits may warrant the use of the drug in pregnant women despite potential risks. In actuality, the safety profile of lamivudine during pregnancy in women has been reported.[31] The Antiviral Pregnancy Registry documents an extensive experience with use of lamivudine during pregnancy, with no evidence for teratogenicity or adverse effects (www.apregistry.com). However, lamivudine is no longer a first-line option for long-term treatment of non-pregnant patients with chronic HBV because of the high rate of lamivudine-resistance (occurring in 15% of patients per year).[57] Lamivudine has been replaced by tenofovir disoproxil fumarate (TDF) or entecavir for treatment of chronic active HBV infection in non-pregnant patients.[20]

TDF may also be the preferred antiviral for HBV infection in pregnancy given its potency, safety profile and better resistance profile than lamivudine.[58] TDF is a pregnancy category B medication; it has been found to be safe in animal models, but with limited data in humans. There are no prospective studies published for the use of TDF in pregnant women with HBV mono-infection; however, it has been safely used in 1731 pregnant women with HIV (some with HBV co-infection), and the rate of birth defects does not significantly differ from pregnancies not exposed to TDF.[31] Given that TDF, 300 mg daily, is a first-line treatment for chronic active HBV infection, its use during the third trimester to prevent HBV transmission is an appropriate option for mothers who need long-term treatment after delivery,[20,31] such as patients with chronic active HBV infection, AST or ALT levels greater than 1.5 to 2 times normal, and an HBV DNA level over 20 000 IU ml $^{-1}$ (5 $\log_{10}$ copies ml^{-1}).[20]

Telbivudine is another category B anti-HBV agent. Recent prospective studies demonstrated the efficacy of telbivudine 600 mg per day in preventing MTCT when used during the second or third trimesters in HBeAg-positive mothers with HBV DNA>200 000 IU ml $^{-1}$ (>6 $\log_{10}$ copies ml $^{-1}$).[53,59] In the controlled trial by Han *et al.*,[53] the incidence of perinatal transmission of HBV infection was significantly lower in infants who completed follow-up born to the telbivudine-treated mothers than to controls (0 vs 8%). No differences in maternal adverse events or fetal congenital deformities were observed at 28 weeks after birth.

The safety of these antiviral agents is established by the Antiviral Pregnancy Registry, which has tracked spontaneously reported maternal and fetal outcomes in women receiving oral nucleoside drugs since 1989. As of 31 January 2008, 9889 pregnancies were reported during which the mother had received an oral nucleoside analogue.[60] The overall prevalence of birth defects in infants exposed to any antiretroviral agent during the first trimester of 3.0 per 100 live births (117 of 3951), or in any trimester of 2.8 per 100 live births (261 of 9400), was not significantly different from that reported in the general US population of 2.72 per 100 live births. Only infants exposed to the anti-HIV medication didanosine had a

significantly higher rate of birth defects than expected. The prevalence of birth defects with lamivudine exposure in the first trimester (3.1%, 85 of 2784) and with TDF (2.2%, 11 of 491) were similar to population controls. The safety data for telbivudine in the Antiviral Pregnancy Registry are limited.[31]

Because of limited data on secretion of antiviral agents into human breast milk, breast feeding is not recommended by the makers of the nucleos(t)ide analogues if antiviral therapy is continued after delivery. There are scanty data on secretion of TDF or its metabolite, tenofovir, into animal or human breast milk. A single small human study found that small amounts of tenofovir, but not TDF, are present in breast milk of HIV-1-infected women taking TDF, representing 0.03% of the proposed oral HIV-prevention dose of tenofovir for infants.[61] Infant exposure to tenofovir through breastfeeding may be negligible because pharmacologically, TDF is converted into its metabolite, tenofovir, prior to excretion of tenofovir into breast milk, and tenofovir is not absorbed by the adult gastrointestinal tract.[62] Therefore, patients should be counseled regarding the scarcity of information on TDF and breastfeeding, as well as the known benefits of breastfeeding, to make an informed breastfeeding decision.

There are a few reports of lactic acidosis and hepatic steatosis in pregnant patients receiving nucleos(t)ide analogues, so monitoring of liver enzymes and electrolytes is recommended.[10] Postpartum flares of hepatitis may occur after stopping lamivudine in patients who receive it during the last 4 weeks of pregnancy.[31,34] For this reason, liver enzymes should be monitored after delivery.

Published guidelines for use of antiviral therapy for HBV in pregnancy—Recent clinical practice guidelines from the European Association for the Study of the Liver (EASL) address antiviral treatment in pregnancy for women with chronic HBV infection (Table 4).[58] It is suggested that women with mild liver disease and low HBV DNA levels (*chronic inactive* HBV infection) complete pregnancy before antiviral treatment is considered; that women with moderate liver disease and no cirrhosis (*chronic active* HBV infection) undergo antiviral treatment and discontinue treatment before pregnancy if there is a viral response; that women with advanced liver disease (*cirrhosis*) receive antiviral treatment before, during and after pregnancy; and that women with mild liver disease and very high HBV DNA levels (*immune-tolerant* chronic HBV infection) receive a category B anti-viral agent (TDF or telbivudine) in the last trimester of pregnancy.[58] The Asian Pacific Association for the Study of the Liver (APASL) also recommends prophylactic antiviral treatment in pregnant women with high levels of viremia.[63]

One of the most commonly cited American clinical guidelines for management of chronic hepatitis B, authored and updated by Keefe *et al.*,[20] states ‘data from clinical studies indicate that women with chronic hepatitis B who have HBV DNA levels>10^7 copies ml $^{-1}$ and elevated ALT levels, or who have had an HBsAg-positive child, are candidates for antiviral therapy because of the increased risk for transmission to the newborn.’

A recent publication proposed ‘an algorithm for risk assessment and patient management that is based on a review of the literature and the opinion of a panel of physicians with

expertise in preventing MTCT'. The authors recommended that pregnant women with chronic HBV infection who are at high risk for MTCT (because of HBV DNA levels >200 000 IU ml $^{-1}$ or >6 $\log_{10}$ copies ml^{-1}, a previous child failed HBIG and HBV vaccine, or who threaten abortion or premature delivery) receive antiviral treatment. The recommended antiviral treatment is lamivudine or telbivudine, or TDF for those with chronic active hepatitis B, beginning in the third trimester of pregnancy.[31] (Figure 3)

Cesarean section for prevention of intrapartum HBV transmission—There has been little evidence that cesarean delivery prevents HBV transmission, and current guidelines do not recommend cesarean section to decrease the risk of MTCT in pregnant women with chronic HBV infection.[21] Cesarean section would have to be performed before the onset of labor or before the rupture of membranes to be effective. A significant reduction in immuno-prophylaxis failure with elective cesarean section for highly viremic mothers was supported by a systematic review and meta-analysis of four randomized trials involving 789 patients.[64] However, it was stated that 'the conclusions of this review must be considered with great caution because of the high risk of bias in each included study (graded C).' Pan *et al.*, [65] analyzed data from 1409 infants born through vaginal delivery, elective cesarean section or urgent cesarean section to HBsAg-positive mothers who completed appropriate immunization against HBV. HBV infection was transmitted to a smaller percentage of infants born by elective cesarean section (1.4%) than by vaginal delivery (3.4%, $P<0.032$) or urgent cesarean section (4.2%, $P<0.020$). Urgent cesarean section had no effect on vertical transmission compared with vaginal delivery ($P = 0.593$), whereas infants born by elective cesarean section had a significantly lower rate of vertical transmission than those born by non-elective cesarean section (1.4 vs 36%, $P = 0.17$). Women with HBV DNA levels<6 $\log_{10}$ copies ml^{-1} did not transmit the infection to their infants, regardless of the method of delivery, and there were no differences in maternal or infant morbidity and mortality among the groups. The authors conclude that elective cesarean sections for HBeAg-positive mothers with levels of HBV DNA ≥6 $\log_{10}$ copies ml^{-1} could reduce vertical HBV transmission.

Prevention of MTCT of HBV in the postpartum period: breastfeeding is safe—Although breast milk contains HBsAg,[66] breastfeeding does not increase the risk of MTCT of HBV. A 1975 study reported a 53% rate of HBV transmission in breastfed infants vs 60% in formula-fed infants.[67] Multiple subsequent studies have shown breastfeeding to be safe for children with mothers with chronic HBV infection. Therefore, the American Academy of Pediatrics states that breastfeeding is not contraindicated.[68] According to the prescribing information, use of lamivudine or TDF is not recommended during breastfeeding, though as discussed above, patients should be counseled regarding the scarcity of information on TDF and breastfeeding, as well as the known benefits of breastfeeding, to make an informed breastfeeding decision.

Postnatal follow-up of mother and infant

HBV-infected mothers should be referred to a Hepatology Clinic for evaluation and follow-up. Therapy is considered for individuals infected with HBV who have elevated liver function tests and viral levels greater than 20 000 IU ml $^{-1}$ (5 $\log_{10}$ copies ml $^{-1}$). Post-

vaccination testing of the infant for HBsAg and HBsAb should be performed after completion of the vaccination series at 9 to 18 months. Testing performed before 9 months can detect HBsAb from HBIG administered during infancy and can miss late HBV infection.

HEPATITIS C IN PREGNANCY

Chronic HCV infection is a major public health problem in the US, accounting for most cases of viral hepatitis in adults and affecting 1 to 2% of the population.[69] Most young women with chronic hepatitis C have no signs or symptoms of liver disease. The prevalence of HCV infection among women of childbearing age in the US is approximately 1%.[70] Prevalence is increased among pregnant women with specific risk factors: intravenous drug use, inhaled drug use, transfusions prior to 1992, homemade tattoos, and HIV infection. The prevalence of HCV infection in pregnant women with intravenous drug use reaches 70 to 95%.[71]

Screening and diagnosis of chronic HCV infection

Routine screening of pregnant women for chronic HCV infection is not recommended because treatment of HCV infection is currently not recommended during pregnancy.[72,73] This recommendation may change in the future as new therapies for HCV come on line, as discussed below. However, at the present time, screening for HCV infection is recommended for the subset of pregnant women with risk factors for HCV exposure[74] (Table 5) because (i) HCV infection is transmitted to neonates, and (ii) postnatal treatment of women with hepatitis C is highly effective.

We recommend that all pregnant women with risk factors for hepatitis C, or with abnormal transaminase levels, undergo screening for antibody to HCV. Polymerase chain reaction (PCR) for detection and quantitation of HCV RNA should be performed if HCV antibody is positive.[7] Only 60 to 70% of young women who are HCV antibody-positive will have active infection with detectable HCV RNA by PCR;[75] 30 to 40% of young women exposed to HCV will spontaneously clear the virus and have no chronic HCV infection. Women who are PCR-positive for HCV RNA are at risk for MTCT, and infants born to these mothers should be screened for HCV infection.

Effect of pregnancy on chronic hepatitis C

Most women with chronic hepatitis C do not develop signs or symptoms of liver disease during pregnancy, and improvement in serum AST and ALT levels may occur.[76] For example, in a series that included 266 HCV RNA-positive pregnant women, the proportion of those with an elevated ALT level decreased from 56% at the beginning of pregnancy to 7% by the third trimester.[76] However, a rise in HCV RNA levels may be noted during the third trimester.[77] The improvement of serum ALT levels despite an increase in HCV RNA levels may be due to a pregnancy-related decrease in the immune response to HCV.[78]

Effect of HCV on pregnancy

As previously noted, after adjusting for sociodemographic variables, large population studies suggest that rates of preterm birth, low birth weight, premature rupture of membranes, gestational diabetes and congenital anomalies are increased with chronic hepatitis C.[5–8,12] Maternal HCV infection is also associated with cholestasis of pregnancy, neonatal abstinence syndrome and neonatal ICU admission.[5,7,12–14]

Cholestasis of pregnancy—Cholestasis of pregnancy (pruritus with elevated serum bile acid levels) has been associated with HCV infection in several studies.[7,13,14] For example, in a large study from New Mexico, cholestasis of pregnancy occurred in 10 of 159 HCV antibody-reactive patients (6.3%), but in none of the 141 HCV antibody-nonreactive patients.[7] In addition, all of the patients with cholestasis were Hispanic, with a 9.3% incidence of cholestasis of pregnancy in Hispanic HCV antibody-reactive pregnant women (10/108). These data are consistent with the reported increased prevalence of cholestasis of pregnancy in Latino populations.[79] Two other studies have demonstrated an association between HCV infection and cholestasis of pregnancy; 15.9% of HCV antibody-positive pregnant women developed cholestasis in one study,[13] while the other found that cholestasis developed in 20.3% of HCV RNA-positive pregnant women.[14]

Preterm birth—Large population studies indicate that chronic HCV infection is associated with preterm birth.[5,8] However, other factors may influence pregnancy outcomes in HCV patients. Drug abuse, alcohol abuse and tobacco use were included in the multivariate statistical analysis in the study by Connell.[5] On the other hand, in the New Mexico study, the incidence of preterm delivery, defined as delivery before 37 completed weeks of gestation, was significantly increased in HCV antibody-positive pregnancies (24.5% compared with 14.9%); however, when multivariate regression was used to adjust for methadone use, tobacco use and prior preterm delivery, there was no significant difference.[7]

Neonatal abstinence syndrome—In the New Mexico study, 84 of 95 neonates (88.4%) born to HCV antibody-positive mothers on methadone had neonatal abstinence syndrome that required weaning, whereas only 12 of 33 neonates (36.4%) born to HCV antibody-negative mothers on similar methadone doses required weaning ($P = 0.001$).[7] Pediatricians should be aware of the high risk of methadone withdrawal for infants born to HCV antibody-positive mothers on methadone.

MTCT of HCV infection

MTCT of HCV occurs in 3 to 10% of pregnancies complicated by maternal HCV infection[71,80] and is the leading cause of pediatric chronic HCV infection.[80] Risk factors for perinatal HCV transmission include higher levels of HCV viremia HIV-HCV co-infection, prolonged rupture of membranes and invasive fetal monitoring (Table 6).

High levels of HCV viremia—Many observational studies indicate that HCV transmission occurs only when women are positive for HCV RNA by PCR testing, and is more likely when mothers have a high HCV RNA level at the time of delivery.[71,80,81] A

recent study found that an HCV RNA level over 600 000 IU ml^{-1} was associated with an increase in MTCT of the virus.[82]

Though the rate of MTCT of HCV infection is not effected by HCV genotype, the rate of HCV chronicity may be higher for infants with HCV genotype 1 than for those with other genotypes, because of less frequent spontaneous viral clearance.[82,83] Recent studies also indicate that there is a relationship between the interleukin 28B (IL28B) genotype and spontaneous clearance of HCV.[84] The IL28B genotype of mother and child does not influence MTCT of HCV infection; however, 83% of infants with the CC genotype exhibited spontaneous HCV clearance vs only 22% of the children with a non-CC genotype.[82]

HIV-HCV co-infection—Maternal co-infection with HIV and HCV is associated with a higher risk of HCV vertical transmission. In HIV-infected pregnant women, the seroprevalence of HCV is 17 to 54%.[85] The risk of HCV transmission is approximately threefold higher in infants born to women co-infected with HCV and HIV,[86,87] ranging from 8.7 to 19%, with lower rates of MTCT associated with highly active antiretroviral therapy.[71] In a large cohort study, HIV co-infected women receiving highly active antiretroviral therapy were no more likely to transmit HCV than those without HIV.[76]

Prolonged rupture of membranes and invasive fetal monitoring—Rupture of membranes greater than 6 h may increase the risk of MTCT of HCV infection, so it is recommended that the second stage of labor be kept short.[74,88] Invasive monitoring of the fetus during labor with a scalp electrode, or exposing the infant to maternal blood infected by HCV because of vaginal or perineal laceration during vaginal delivery, increases the risk of perinatal transmission of HCV.[88,89] Thus, avoidance of internal fetal monitoring in HCV-infected women is recommended.[74,88]

Cesarean section does not prevent HCV transmission—Delivery by cesarean section does not reduce the risk of transmission of HCV from HCV-positive, HIV-negative mothers; consensus statements and guidelines do not recommend cesarean section for these patients.[74,90,91] However, observational studies have been under-powered and have not distinguished between elective pre-labor cesarean section and emergency cesarean section after the onset of labor.[92] Many of the cesarean sections in observational studies occurred in HIV co-infected women and/or during labor after rupture of amniotic membranes.[71,75,92] One study has suggested that HCV transmission may be reduced if infants are delivered by cesarean section prior to rupture of membranes.[93] In contrast, a recent meta-analysis of eight studies with 641 mother–infant pairs[94] and the large European Paediatric HCV Network study[91] suggest that cesarean section does not decrease perinatal HCV transmission from HCV RNA-positive, HIV-negative mothers to infants. There are no randomized controlled trials of cesarean section vs vaginal delivery for preventing MTCT of HCV infection.

Breastfeeding and HCV transmission—There is no evidence that breastfeeding is a risk for MTCT of HCV infection.[90] In one study, none of 76 samples of breast milk from HCV antibody-positive mothers contained HCV RNA, while 60% of the mothers tested had HCV viremia.[95] Other studies show no evidence of transmission with breastfeeding; either

similar rates of infection are observed in breastfed and bottle-fed infants, or no viral transmission is documented.[96–98] The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics support breastfeeding by HCV-infected mothers.[99]

Prevention of MTCT of HCV infection

Until recently, standard HCV treatment has been with pegylated-interferon and ribavirin. Although young women generally respond well to treatment, ribavirin is considered teratogenic (pregnancy category X), and interferon has been associated with intrauterine growth restriction (pregnancy category C). Thus, treatment is not recommended for use in pregnancy or as a prophylactic in newborns. As such, there has been a critical need for new treatment options that do not have these adverse effects.

For patients who are not pregnant, antiviral therapy for HCV has become less toxic and more efficacious. Until recently, recommendations for HCV treatment were pegylated interferon plus ribavirin for genotype 2 or 3 HCV infection, and a three-drug regimen (pegylated interferon injection with oral ribavirin plus a protease inhibitor such as boceprevir or telaprevir) for genotype 1 HCV infection. However, the Food and Drug Administration has recently approved a new once/day protease inhibitor, simeprevir, as well as sofosbuvir, an oral HCV polymerase inhibitor. These interferon-free regimens have been in use since January 2014, but have not been studied for use during pregnancy.[100–104] The question of HCV treatment with these new medications during pregnancy, now not recommended, will surface. Treatment of HCV-infected pregnant women might be envisioned in the future if non-teratogenic regimens are developed, which could further reduce the up to 10% risk of MTCT and the long-term health burden of HCV infection resulting from vertical transmission.

Diagnosis of HCV infection in the newborn

Infants born to women with chronic hepatitis C have maternal anti-HCV antibodies that can be detected until 12 to 15 months of life. Chronic hepatitis C infection in infancy is diagnosed by the presence of HCV RNA by PCR testing at 3 to 6 months of age or by detectable HCV antibody at age 18 months. Therefore, appropriate infant follow-up after birth for testing is needed to detect HCV MTCT.

Postnatal follow-up of mothers

Postnatal follow-up for chronic hepatitis C is particularly important because the new generation of oral anti-HCV medications, used for 12 weeks for genotypes 1 or 2 HCV and for 24 weeks for genotype 3 HCV, can achieve sustained viral response rates over 90%.[105,106] These patients should be referred for treatment of hepatitis C once they have completed breastfeeding.

HBV AND HCV IN PREGNANCY: SUMMARY AND RECOMMENDED GUIDELINES FOR TREATMENT

Antiviral therapy with TDF or telbivudine beginning at 32 weeks of gestation should be strongly considered for women with high HBV DNA levels (>200 000 IU ml^{-1} or 6 $\log_{10}$

copies ml^{-1}) to decrease the rate of MTCT of HBV infection (*Level A*) (Table 7). All infants born to HBsAg-positive mothers should receive HBIG and HBV vaccine as early as possible, no later than 12 h after birth (*Level A*). Newborns of mothers with unknown hepatitis B status should also receive immunoprophylaxis (*Level C*). The vaccine series should be completed according to recommended schedules.[107] Current guidelines do not recommend elective cesarean delivery for mothers with chronic HBV infection (*Level B*); however, a recent nonrandomized study showed elective cesarean section may decrease vertical transmission of HBV if the HBV DNA level is >20 million IU ml^{-1} (> 6 $\log_{10}$ copies ml^{-1}) at term. [65] Breast feeding does not increase MTCT of HBV and is not contraindicated (*Level B*), though breast feeding is not recommended during maternal antiviral therapy by drug manufacturers (*Level C*).

We recommend that all pregnant women with risk factors for hepatitis C or with abnormal ALT levels undergo screening for antibodies to HCV; if positive, PCR for quantitation of HCV RNA level should be performed (*Level B*). Women who are PCR-positive for HCV are at risk for MTCT of HCV, and infants born to these mothers should be screened for HCV infection (*Level B*). Women with HCV infection are at an increased risk for cholestasis of pregnancy (*Level B*). HCV-infected women on methadone have an increased risk for preterm birth, while their infants have a high incidence of neonatal withdrawal syndrome (*Level C*). Unlike HBV, patients are typically not treated for HCV during pregnancy. However, young women are ideal candidates for treatment of HCV infection in the postpartum period, with a greater than 90% chance of resolving the infection with less toxic and more efficacious new regimens (*Level A*).

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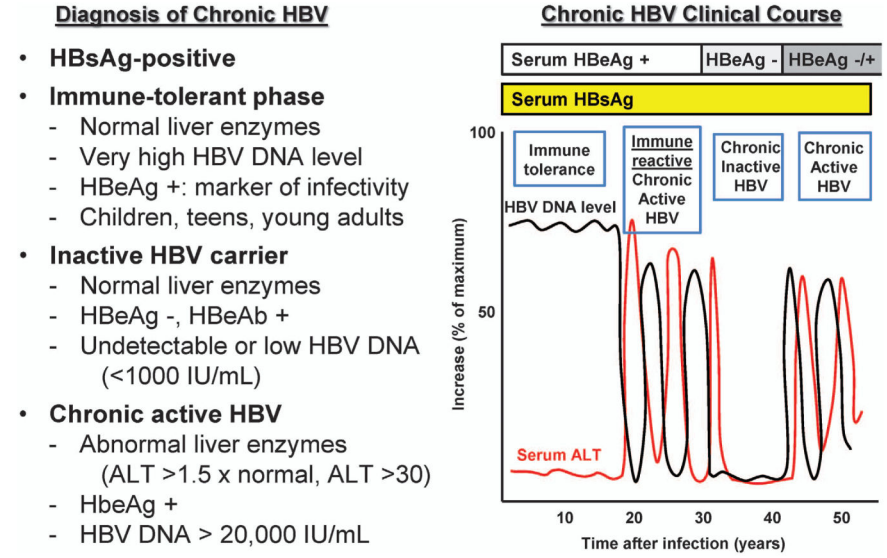

Figure 1.

Phases of chronic HBV infection. In the immune-tolerant phase of chronic HBV infection, ALT levels are normal whereas HBV DNA levels are markedly elevated. In the immune-reactive or chronic active phases, ALT and HBV DNA levels are elevated. In chonic inactive phases of HBV infection, ALT and HBV DNA levels are decreased; <1000 IU ml^{-1} is equivalent to <6 × 3 $\log_{10}$ copies ml^{-1}; >200 000 IU ml^{-1} is>6 $\log_{10}$ copies ml^{-1}.

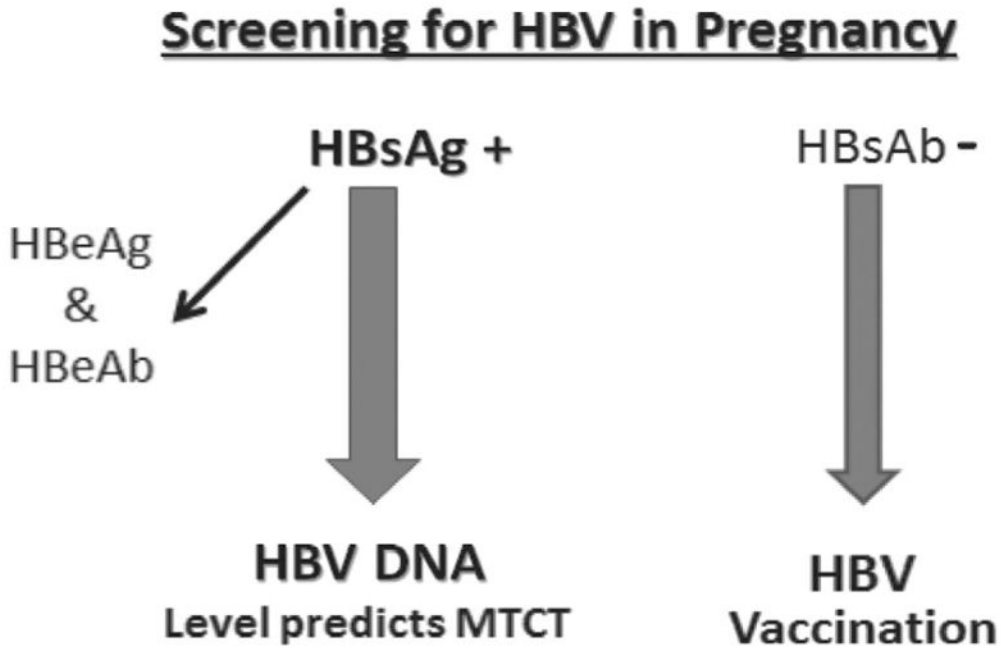

Figure 2.
HBsAg is checked in all pregnant women. HBsAg-positive patients should have HBV DNA level and HBeAg checked. We recommend checking HBsAb and immunizing HBsAb-negative patients.

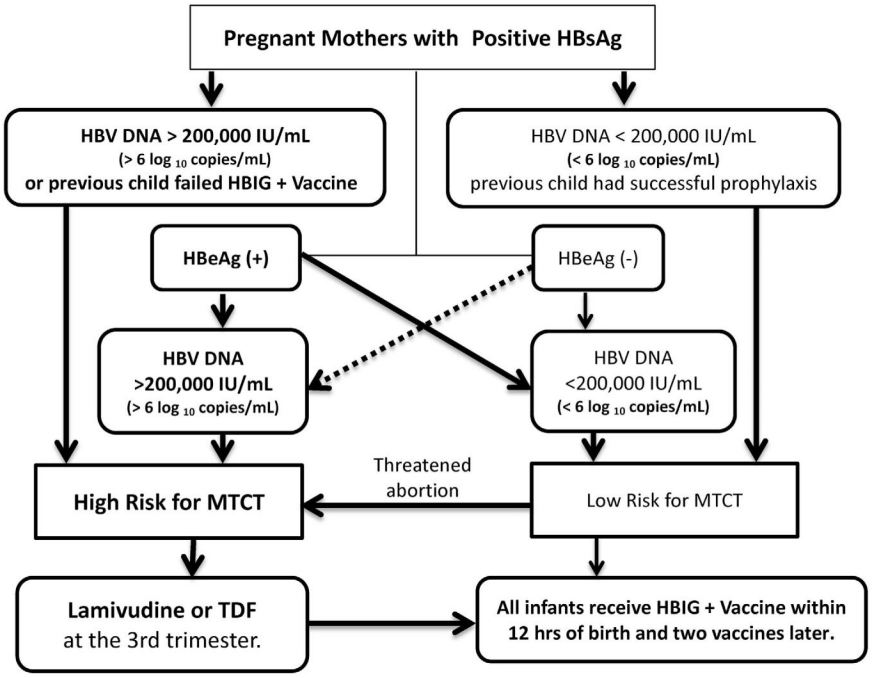

Figure 3.

Pregnant women with HBV DNA levels >200 000 IU ml^{-1} (>6 $\log_{10}$ copies ml^{-1}), or any HBsAg-positive woman with a threatened abortion, are at high risk for MTCT and should receive antiviral treatment in the third trimester.[31]

Table 1

Pregnancy outcomes with HBV and HCV

HBV and HCV
Preterm birth
Low birth weight
Premature rupture of membranes
Gestational diabetes
Possible small increase in congenital anomalies
HCV
Cholestasis of pregnancy
NICU admission
Neonatal abstinence syndrome

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus. References: 5–14.

Table 2

Diagnosis of hepatitis B

Serologic markers	Clinical significance
HBcAb IgM (Hepatitis B core antibody IgM)	Acute infection
HBeAg (Hepatitis B e antigen)	High infectivity
HBeAb (Hepatitis B e antibody)	Low infectivity
HBsAb (Hepatitis B surface antibody)	Immunity
HBcAb IgG and HBsAg	Chronic infection
HBcAb IgG and HBsAb	Resolved infection
HBV DNA level (May be undetectable in chronic inactive HBV infection)	Acute or chronic infection

Abbreviations: HBV, hepatitis B virus.

Table 3

Immunoprophylaxis of neonates with HBIG+HBV vaccine is superior to monotherapy with either agent alone for prevention of MTCT of HBV infection

	HBV vaccine	HBIG	HBIG+HBV vaccine
MTCT of HBV	26–36%	15–20%	5–10%[a]

Abbreviations: HBIG, hepatitis B immune globulin; HBV, hepatitis B virus; MTCT, mother-to-child transmission. References: 23, 47.

[a] A major risk for immunoprophylaxis failure is maternal HBV DNA level >200 000 IU ml^{-1} (>6 $\log_{10}$ copies ml^{-1}).

Table 4

European Association for Study of the Liver (EASL) recommendation for antiviral therapy for HBV-infected women who desire pregnancy[a]

Mild liver disease, low viremia (chronic inactive HBV)	→ Pregnancy before treatment
Moderate liver disease, no cirrhosis (chronic active HBV)	→ Treatment before pregnancy; if responds, stop treatment before pregnancy
Advanced liver disease (advanced fibrosis-cirrhosis)	→ Treatment before, during and after pregnancy
Mild liver disease, very high viremia (immunotolerant)	→ Treatment in last trimester with a 'B' category drug with post-partum discontinuation

Abbreviations: HBV, hepatitis B virus.

[a] Adapted from the EASL Clinical Practice Guidelines, Ref. 58.

Table 5

Indications for HCV screening in pregnancy

Exposure to blood products before 1992
History of intravenous drug use
Dialysis patients
HIV or HBV infection
Sexual partners of people with HIV, HBV or HCV
History of body piercing or tattoos
Organ transplant before 1992
Unexplained elevation of AST or ALT
Involved in *in vitro* fertilization from anonymous donors
History of incarceration

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; HBV, hepatitis B virus, HCV, hepatitis C virus.

Table 6

MTCT of HCV

Occurs in 3–10% of HCV-infected mothers.
Is leading cause of pediatric chronic HCV.
Risk factors
Level of HCV viremia (>600 000 IU ml^{-1})
HIV-HCV co-infection: increased fourfold
Prolonged rupture of membranes (>6 h)
Invasive fetal monitoring, scalp electrodes
C-section does not decrease risk.

Abbreviations: HCV, hepatitis C virus; MTCT, mother to child transmission.

Table 7

Grading system for recommendations

Level of evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.