Hepatitis B and pregnancy

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INTRODUCTION

Hepatitis B virus (HBV) infection during pregnancy presents with unique management issues for both the mother and the fetus. These include the effects of HBV on maternal and fetal health, the effects of pregnancy on the course of HBV infection, treatment of HBV during pregnancy, and prevention of mother-to-child transmission.

Prevention of mother-to-child transmission is an important component of global efforts to reduce the burden of chronic HBV since vertical transmission is responsible for approximately one-half of chronic infections worldwide. The risk of developing chronic HBV infection is inversely proportional to the age at time of exposure. The risk is as high as 90 percent in those exposed at birth without vaccination, while the risk is much lower (about 20 to 30 percent) in those exposed during childhood. Maternal screening programs and universal vaccination of infants have significantly reduced transmission rates.

This topic will review special considerations for the management of patients with acute and chronic HBV infection during pregnancy and the postpartum period, as well as prevention of mother-to-child transmission.

We recognize that not all pregnant, postpartum, and lactating individuals identify as women or mothers. Using gender-inclusive language, however, is not possible in all languages and all countries and for all our readers. The topics discussed here are based on risks driven by biological sex and not gender identify. Therefore, throughout this topic, we use the term

"woman" to signify a person of the female sex (regardless of gender identity) and the term "mother" to signify the female biological parent of a child (regardless of gender identity).

Additional topic reviews that address prevention and management of HBV infection in children, and liver disease in pregnancy, are found elsewhere:

- (See "Hepatitis B virus immunization in infants, children, and adolescents".)
- (See "Hepatitis viruses and the newborn: Clinical manifestations and treatment".)
- (See "Clinical manifestations and diagnosis of hepatitis B virus infection in children and adolescents" and "Management of hepatitis B virus infection in children and adolescents".)
- (See "Acute fatty liver of pregnancy".)
- (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)
- (See "Intrahepatic cholestasis of pregnancy".)
- (See "Approach to evaluating pregnant patients with elevated liver biochemical and function tests".)
- (See "Pregnancy in women with pre-existing chronic liver disease".)

ACUTE HEPATITIS B VIRUS INFECTION

Acute viral hepatitis is the most common cause of jaundice in pregnancy [1]. Other causes include liver diseases associated with pregnancy, such as acute fatty liver of pregnancy, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and intrahepatic cholestasis of pregnancy. (See "Approach to evaluating pregnant patients with elevated liver biochemical and function tests" and "Acute fatty liver of pregnancy" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)" and "Intrahepatic cholestasis of pregnancy".)

Acute hepatitis B virus (HBV) infection during pregnancy is usually mild and not associated with increased mortality or teratogenicity [1,2]. Thus, infection during gestation should not prompt consideration of termination of the pregnancy. However, there have been reports of an increased incidence of low birth weight and prematurity in infants born to mothers with acute HBV infection [2,3].

Acute HBV infection occurring early in the pregnancy has been associated with a 10 percent perinatal transmission rate [3]. Transmission rates significantly increase if acute infection occurs at or near the time of delivery, with rates as high as 60 percent reported [1]. Thus, serial monitoring should be performed throughout pregnancy, and if the mother remains hepatitis B surface antigen (HBsAg) positive or has detectable serum HBV DNA, the infant should receive

hepatitis B immune globulin in addition to the first dose of the hepatitis B vaccine at birth. Antiviral therapy to reduce maternal viral load should also be considered if the mother has high serum HBV DNA levels near the time of delivery. (See 'Prevention of mother-to-child transmission' below.)

Treatment of acute infection is mainly supportive. Liver biochemical tests and prothrombin time should be monitored. Antiviral therapy is usually unnecessary, except in women who have acute liver failure or protracted severe hepatitis [4]. (See "Hepatitis B virus: Overview of management", section on 'Acute infection'.)

For those with acute HBV infection who require antiviral therapy, the choice of which agent to use should be based upon the predicted duration of treatment and the accessibility and cost for the patient. Tenofovir disoproxil fumarate (TDF) (300 mg daily) or lamivudine (100 mg daily) are both suitable options in this setting because both have been safely used during pregnancy, and the risk of developing resistance is low since the duration of treatment is expected to be short [5]. However, we prefer TDF as there is less risk of resistance. A more detailed discussion of the safety of antiviral agents for the treatment of HBV during pregnancy is found below. (See 'Safety of antiviral agents in pregnancy' below.)

CHRONIC HEPATITIS B VIRUS INFECTION

Impact of pregnancy on the natural history of chronic HBV — Pregnancy is generally well tolerated in women with chronic hepatitis B virus (HBV) infection who do not have advanced liver disease. However, pregnancy is considered to be an immune-tolerant state and is associated with high levels of adrenal corticosteroids that may modulate immune response. Thus, the following clinical manifestations may be seen in pregnant women with chronic HBV:

- **Hepatic flares** – The immunological changes during pregnancy and the postpartum period have been associated with hepatitis flares (including hepatic decompensation); however, flares with serious clinical sequelae appear to be uncommon [6,7]. A flare of HBV infection is typically defined as a greater than two- to threefold rise in the alanine aminotransferase (ALT) that is at least three to five times above the reference range. During the postpartum period, flares may be related to immune reconstitution, a situation immunologically analogous to flares that have been described following the withdrawal of immunosuppressive medications in nonpregnant patients with chronic HBV [8-10].

  In a prospective study that followed 126 women during pregnancy and the postpartum period, two patients developed a flare during pregnancy whereas 27 (25 percent)

developed a flare in the postpartum period [7]. A subsequent retrospective study of 310 pregnant women in the United States with 388 pregnancies found the incidence of hepatitis flares to be low and similar during pregnancy and within six months postdelivery (14 and 16 percent, respectively), although this study was limited by a high percentage of women with missing hepatitis B e antigen (HBeAg) and HBV DNA during pregnancy and a high percentage with missing ALT postpartum [11].

Predictors of HBV flares during pregnancy have not been established. However, flares appear to be more common in women who are HBeAg positive [7,11]. In addition, flares have been associated with HBeAg seroconversion in approximately 12 to 17 percent of patients [8], a rate similar to what has been described in patients who are not pregnant. Limited evidence suggests that seroconversion is unrelated to maternal age, parity, or the presence of precore or basal core promotor mutations [8,12]. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Immune-active, HBeAg-negative'.)

- **Progression of liver disease** – The immunologic, metabolic, and hemodynamic changes that occur during pregnancy have the potential to worsen or unmask underlying liver disease. Although progression to cirrhosis is not expected within such a short time for most patients, decompensation can occur in the setting of a severe flare.

  However, it can be difficult to assess the progression of liver disease during pregnancy because of normal physiologic changes that can mimic clinical features of chronic liver disease. In particular, serum albumin and hematocrit often decrease, while alkaline phosphatase and alpha fetoprotein increase. Similarly, physical examination may reveal findings suggestive of stigmata of chronic liver disease such as palmar erythema, lower extremity edema, and spider angiomata.

- **HBV DNA** – The immunologic changes associated with pregnancy also have the potential to increase HBV viremia; however, most studies have found that HBV DNA levels remain stable during pregnancy [13,14].

Effect of chronic HBV on pregnancy outcomes — For mothers with chronic HBV, the impact of HBV infection on newborns is not well defined and data are conflicting [15-23]. As an example, one large study compared 824 hepatitis B surface antigen (HBsAg)-positive women with 6281 HBsAg-negative controls [19]. No differences were seen in gestational age at delivery, birth weight, incidence of prematurity, neonatal jaundice, congenital anomalies, or perinatal mortality. However, other studies have found possible associations between chronic HBV and gestational diabetes mellitus [15,16,20], increased risk of prematurity [21], lower birth weight [22], and antepartum hemorrhage [20].

Women with cirrhosis are at significant risk for perinatal complications and poor maternal and fetal outcomes [23], including intrauterine growth restriction, intrauterine infection, premature delivery, and intrauterine fetal demise. The increased risk was demonstrated in a population-based study in Canada, which compared maternal and fetal outcomes in 399 patients with cirrhosis to a matched control group who delivered between 1993 and 2005 [24]. Maternal complications including gestational hypertension, placental abruption, and peripartum hemorrhage were increased in the group with cirrhosis. In addition, 15 percent of mothers with cirrhosis developed hepatic decompensation. Overall mortality was significantly higher than controls (1.8 versus 0 percent). Infants born to mothers with cirrhosis also had higher rates of prematurity and growth restriction and significantly higher rates of fetal mortality (5.2 versus 2.1 percent). Other reports have described an increased risk of variceal bleeding, particularly during the third trimester and during labor because of increased intra-abdominal pressure and plasma volume expansion. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Cirrhosis and portal hypertension'.)

A discussion of mother-to-child transmission is found below. (See 'Mother-to-child transmission' below.)

Management considerations — Various factors need to be assessed when determining the management of pregnant women with chronic HBV during pregnancy, including the indications for treatment, the anticipated duration of therapy, the potential adverse effects to the fetus, the risk of developing drug resistance, and the accessibility and cost of the antiviral agents. The health of the mother and fetus must be considered independently when deciding on treatment. Pregnant women with chronic HBV should be managed in conjunction with a hepatologist.

Patients who are pregnant — Some patients with chronic HBV require antiviral therapy to prevent progression of liver disease (eg, those with immune-active hepatitis), while others can be observed.

- **Patients who become pregnant while receiving antiviral therapy** – Women should inform their clinician immediately if they become pregnant while receiving antiviral therapy, and the risks and benefits of continuing treatment should be discussed. Continuing treatment may pose a risk to the fetus while discontinuing treatment may pose a risk of hepatitis flare for the mother.

  Discontinuing treatment can be considered in women without cirrhosis if the patient has achieved a therapeutic endpoint (see "Hepatitis B virus: Overview of management", section on 'Duration and treatment endpoints'). Otherwise, women receiving entecavir, adefovir, interferon, or tenofovir alafenamide (a formulation of tenofovir that was

approved in 2016) can continue treatment by switching to an alternative agent, such as tenofovir disoproxil fumarate (TDF), which has more safety data available and appears to be safe for use in pregnancy. These women should be monitored closely during the transition period to ensure viral suppression. A more detailed discussion of the safety of antiviral agents during pregnancy is found below. (See 'Safety of antiviral agents in pregnancy' below.)

- **Indications for antiviral therapy** – The decision to initiate therapy while pregnant depends upon the presence or absence of cirrhosis, HBeAg, and hepatitis B e antibody (anti-HBe), as well as the HBV DNA and aminotransferase levels [25]. (See "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy' and "Hepatitis B virus: Overview of management".)

  The indications for antiviral therapy in pregnant women are generally the same as those for patients who are not pregnant. Antiviral therapy is recommended for patients with a persistently elevated ALT >2 times the upper limit of normal and an elevated HBV DNA (HBV DNA >20,000 international units/mL in HBeAg-positive patients or HBV DNA ≥2000 international units/mL in HBeAg-negative patients) (table 1).

  However, for those without cirrhosis, some scenarios may differ. As examples:

  - During pregnancy, a person may choose to defer therapy until after delivery if there is only evidence of mild disease activity, such as aminotransferase levels just above the treatment threshold.

  - By contrast, a person with a viral load >2 x 10^5 international units/mL during pregnancy should initiate therapy in the third trimester, even if the aminotransferase levels are normal. In this setting, the goal of therapy is to prevent transmission to the child. The use of antiviral therapy to prevent maternal fetal transmission is discussed below. (See 'Maternal antiviral therapy to prevent transmission' below.)

  TDF is preferred if antiviral therapy is contemplated during pregnancy because of its potency; safety profile, including use during first trimester; and low risk of resistance. There is accumulating data that tenofovir alafenamide may also be safe in pregnancy [26-28]. (See 'Maternal antiviral therapy to prevent transmission' below and 'Safety of antiviral agents in pregnancy' below.)

- **Monitoring those without indications for antiviral therapy** – Women who are not on antiviral therapy during pregnancy should be monitored closely to evaluate for a flare (see 'Impact of pregnancy on the natural history of chronic HBV' above):

- We obtain liver biochemical tests every three months during pregnancy and for up to six months postpartum. Thereafter, monitoring will be the same as for other hepatitis B patients not requiring antiviral therapy, generally every six months for HBeAg-positive patients in the immune tolerant phase and every 6 to 12 months for those who are confirmed to be in the inactive carrier phase (table 2). (See "Hepatitis B virus: Overview of management".)

- HBV DNA should be tested concurrently or when there is ALT elevation. In addition, the HBV DNA should be measured at 26 to 28 weeks to determine if antiviral therapy should be offered to reduce the risk of mother-to-child transmission. (See 'Maternal antiviral therapy to prevent transmission' below.)

- **Patients with cirrhosis** – The management of cirrhosis in a pregnant woman does not differ from that of nonpregnant patients. Variceal screening with endoscopy is still recommended and is safe during pregnancy. Active variceal bleeding should be managed the same way with banding. Indications for use of beta blockade for prophylactic or postvariceal bleeding management is the same as in nonpregnant individuals, but the use of beta blockers is associated with a small increase in risk of intrauterine growth restriction, fetal/neonatal bradycardia, neonatal hypoglycemia, and/or neonatal respiratory depression. Octreotide should not be given during management of acute variceal bleeding because of the risk of uterine ischemia. A more detailed discussion of the management of pregnant women with cirrhosis is found elsewhere. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Cirrhosis and portal hypertension'.)

Patients with childbearing potential — Indications for antiviral therapy are the same as those for patients who do not have childbearing potential. They are determined by the HBeAg status, the HBV DNA level, and the activity or stage of liver disease. (See "Hepatitis B virus: Overview of management".)

However, there are important considerations in women of child-bearing potential:

- Those with mild liver disease who are planning to conceive in the near future may choose to defer treatment and be observed until they have completed childbearing.

- Those who elect to undergo treatment before attempting pregnancy may opt for pegylated interferon because of its finite duration (48 weeks), provided they use contraception during treatment. However, if the patient chooses treatment with a nucleos(t)ide analogue, TDF is preferred because it has been shown to be safe in

pregnancy, and the risk of drug resistance is low. (See 'Safety of antiviral agents in pregnancy' below.)

- Patients who become pregnant while on therapy should contact their provider immediately. The management of such patients is described above. (See 'Patients who are pregnant' above.)

Breastfeeding — Infants who received hepatitis B immune globulin (HBIG) and the first dose of hepatitis B vaccine at birth can be breastfed [23,29]. However, it is important that the infant complete the hepatitis B vaccine series. Mothers with chronic hepatitis B who are breastfeeding should also exercise care to prevent bleeding from cracked nipples. HBsAg-positive mothers should not participate in donating breast milk. Discussions of breastfeeding and HBV transmission and newborn immunization are found below. (See 'Breastfeeding and transmission' below and 'Newborn immunization' below.)

For women with chronic HBV who continue antiviral treatment after delivery, the safety data on the use of HBV antiviral therapy during breastfeeding is unclear. Thus, the benefits of breastfeeding, and the availability of alternatives to breastfeeding, should be discussed with women who require postpartum antiviral therapy. The decision to breastfeed should be based upon patient preference.

Drug labels have typically recommended that nucleos(t)ide analogues be avoided during breastfeeding because they are excreted into the breastmilk. However only low levels of tenofovir are detected among women receiving TDF [30-34], and these are unlikely to have any biologic effects on the nursing infant. As an example, one study found that the median breastmilk dose from mothers receiving TDF represented 0.03 percent of the proposed oral infant dose and simulated neonatal plasma concentrations were extremely low [32]. Another study found that the ratio of tenofovir concentration in breast milk to that in maternal plasma was 0.07 and none of the infants had detectable tenofovir in their plasma [35]. In addition, case reports of infants born to mothers with chronic HBV found no short-term adverse effects in infants who were breastfed while their mothers received TDF [36-39].

Data from HIV-infected women also support the safety of antiviral therapy during breastfeeding. As an example, a study evaluating tenofovir and emtricitabine in the breastmilk of five HIV-infected women in Africa found that the median amount of tenofovir and emtricitabine ingested via breastfeeding would be 0.03 and 2 percent, respectively, of the proposed oral infant doses [32]. Additional discussions of breastfeeding in HIV-infected patients are found elsewhere. (See "Prevention of HIV transmission during breastfeeding in resource-

limited settings" and "Antiretroviral selection and management in pregnant individuals with HIV in resource-rich settings".)

MOTHER-TO-CHILD TRANSMISSION

Mother-to-child transmission accounts for most of the burden of chronic HBV. The World Health Assembly adopted the Global Health Sector Strategy (GHSS) on viral hepatitis in 2016, calling for elimination of viral hepatitis B and C by 2030 [40]. Administering the HBV birth dose vaccination (HepB-BD) and completing the three-dose vaccination series are the most important interventions in eliminating mother-to-child transmission. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Routine infant immunization'.)

Risk of transmission — The risk of mother-to-child transmission of hepatitis B virus (HBV) from hepatitis B surface antigen (HBsAg)-positive mothers to their infants has been reported to be as high as 90 percent without the use of active and passive immunization [41]. Transmission can occur in utero, at birth, or after birth. (See 'Risk factors for transmission' below and 'Prevention of mother-to-child transmission' below.)

However, the risk of HBV transmission has been significantly reduced with the introduction of universal maternal HBV screening, hepatitis B vaccination of all newborns, and the use of prophylactic hepatitis B immune globulin (HBIG) for infants of HBsAg-positive mothers. As an example, perinatal HBV infection occurred in 1.1 percent of newborns in a cohort study that evaluated 9252 infants born to HBsAg-positive mothers in the United States [42]. Approximately 95 percent of infants received hepatitis B vaccine and HBIG within 12 hours of birth and almost all completed ≥3 doses of the hepatitis B vaccine series. Transmission was significantly associated with having a mother who was hepatitis B e antigen (HBeAg) positive, had a HBV viral load >2000 international units/mL, or was <25 years old; transmission was also associated with receiving <3 doses of the hepatitis B vaccine series. In this study, the association between younger maternal age and HBV transmission may have been related to the mother's HBeAg status and viral load, since younger women in the cohort were more often HBeAg positive with higher HBV DNA levels, consistent with immune tolerant phase, compared with older women.

The high protective efficacy of neonatal vaccination suggests that most infections occur at birth when maternal secretions and blood in the birth canal come into contact with the infant's mucosal membranes. In support of this hypothesis, a study performed in China found that only 3.7 percent of babies who tested positive for HBsAg at birth were infected through intrauterine transmission [43].

Risk factors for transmission — The most important risk factors for mother-to-child transmission, despite proper administration of prophylaxis (HBIG and first dose of hepatitis B vaccine given within 12 hours of birth and completion of hepatitis B vaccine series), appear to be a positive HBeAg and/or a high HBV DNA level in the mother.

Transplacental transmission and transmission due to obstetrical procedures are infrequent causes, and breastfeeding does not appear to pose a substantial risk. In addition, the benefit of cesarean delivery in protecting against transmission has not been clearly established. Thus, the obstetrical approach should not be influenced by the HBV status of the mother.

HBV replicative status — The risk of transmission is increased in women who are HBeAg positive and/or have high levels of HBV DNA. In one series, transmission occurred in the absence of prophylaxis in 85 to 90 percent of infants born to HBeAg-positive mothers and 32 percent of infants born to HBeAg-negative mothers [44]. Children born to HBeAg-positive mothers remain at risk for HBV infection, even if they receive hepatitis B vaccination and HBIG (approximately 9 percent in one large cohort study) [45]. A description of the replicative phases of chronic HBV infection is found elsewhere. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Phases of chronic HBV infection'.)

HBV DNA level — Maternal serum HBV DNA levels correlate with the risk of transmission. Vertical transmission of hepatitis B occurs in 9 to 39 percent of infants of highly viremic mothers despite postnatal vaccination [46-50]. The risk of HBV transmission is rare when maternal HBV DNA is $<10^5$ to 10^6 international units/mL. As examples:

- In a study of 773 HBsAg-positive mothers in Taiwan, the odds ratio for having an infected infant increased from 1 to 147 as the maternal serum HBV DNA levels increased from 5 pg/mL (approximately 150,000 international units/mL) to >1400 pg/mL (approximately 45,000,000 international units/mL) [51].

- In another study conducted in China involving 112 newborns of mothers with chronic HBV infection, the rate of infection increased from 0 percent in mothers with serum HBV DNA levels <20,000 international units/mL ($<10^5$ copies/mL) to 50 percent in those with HBV DNA levels approximately 10^9 international units/mL (between 9 and 10 $\log_{10}$ copies/mL) [52].

- A study conducted in Australia that included 138 babies born to HBV DNA-positive mothers showed a similar trend [53]. HBV transmission was detected in four babies despite the use of HBIG and hepatitis B vaccination in three and the use of vaccine alone in one. All four babies were born to mothers with high HBV DNA levels ($>10^8$ copies/mL).

- A prospective observational study followed 303 mother-infant pairs in which the mother was HBsAg positive [54]. Chronic HBV infection developed in 10 infants born to the 87 HBeAg-positive mothers whereas none of the infants born to the 216 HBeAg-negative mothers became infected. All of the infants born to HBeAg-positive mothers received a dose of hepatitis B vaccine within the first week and HBIG within 24 hours of birth. A multivariable logistic regression model predicted rates of maternally transmitted HBV infection at HBV DNA levels of 2×10^4, 2×10^5, 2×10^6, 2×10^7, and 2×10^8 international units/mL to be 0.9 percent (95% CI, 0.9–2.7 percent), 2.6 percent (95% CI, 1.1–6.2 percent), 6.6 percent (95% CI, 0.5–12.6 percent), 14.6 percent (95% CI, 5.6–23.6 percent), and 27.7 percent (95% CI, 13.1–42.4 percent) respectively.

- An observational study evaluated 4446 infants born to 3253 HBV-positive mothers between 1997 and 2010 [55]. The majority of infants received HBIG and three doses of the hepatitis B vaccine. Mother-to-child transmission occurred in 3.4 percent of births to HBeAg-positive mothers and 0.04 percent of births to HBeAg-negative mothers. HBV DNA and HBeAg testing was available in 835 women. Among such women, three infants acquired HBV infection despite passive and active immunization. All three children were born to mothers who were HBeAg-positive and had an HBV DNA level >6×10^7 international units/mL. No HBV transmission occurred in mothers with viral loads less than 5×10^7 international units/mL, regardless of the mother's HBeAg status.

- A meta-analysis that included 13 studies found that among infants who received a timely birth dose (within 12 hours) of HBIG and HBV vaccine, none were infected when maternal HBV DNA was <200,000 international units/mL [56].

Transplacental transmission — Transplacental transmission appears to cause only a minority of infections. It can occur due to leakage, such as during a threatened abortion [57,58]. HBV has been found in the villous capillary endothelial cells and the trophoblasts of the placenta [43,59]. This supports the hypothesis that breach of the placental barrier is a possible mechanism for intra-uterine infection. As a result, when preterm labor or spontaneous abortion occurs, there may be mixing of maternal and fetal blood, which may result in HBV transmission [57]. One study found that HBV is able to translocate through the placenta from the mother to the fetal trophoblast [60]. The causes of transplacental infection are unclear. High maternal viral load and preterm labor have been described as risk factors, but the strength of these associations is uncertain [43,52,61].

Amniocentesis and other procedures — Diagnostic amniocentesis, if clinically indicated, should not be withheld. Transmission following amniocentesis has been described, but the risk appears to be low [62], particularly if the mother is HBeAg negative with a low HBV viral load,

and the procedure is done using a 22-gauge needle under continuous guidance [63,64]. (See "Diagnostic amniocentesis".)

Most studies do not demonstrate an increased risk for in utero infection after amniocentesis in women with chronic HBV infection. In an illustrative study, women with HBV who underwent amniocentesis had a rate of vertical transmission that did not differ significantly from women with HBV who did not undergo amniocentesis (9 versus 11 percent) [65]. However, one study found an increased risk when the maternal HBV DNA was >7 log international units/mL [66].

The Society for Maternal-Fetal Medicine recommends that for women with HBV who have an indication for genetic testing, invasive testing (eg, amniocentesis or chorionic villus sampling) may be offered; patients should be counseled that the risk for mother-to-child transmission of HBV may be increased with maternal HBV DNA >7 log international units/mL [23].

Preterm premature rupture of membranes — There are limited data that have examined preterm premature rupture of membranes as a risk factor for HBV transmission, and the available data are conflicting [67,68]. As a result, management of such patients should not differ from that of women with chronic HBV without preterm premature rupture of membranes.

Cesarean delivery — The benefit of cesarean delivery in protecting against HBV transmission has not been clearly established in well-conducted controlled trials, and available data are conflicting [69-73]. Thus, cesarean delivery is not routinely recommended for carrier mothers for the sole purpose of reducing HBV transmission [23,74].

Breastfeeding and transmission — Transmission of HBV through breastfeeding is unlikely, particularly in infants who received HBIG and hepatitis B vaccine at birth. Although HBV DNA has been detected in the colostrum of HBsAg-positive mothers, a study of 147 infants born to carrier mothers revealed no evidence of a relationship between breastfeeding and the subsequent development of chronic HBV infection in the babies [75]. In another study involving 369 neonates born to mothers with chronic HBV infection, of whom all received and completed the HBV immunoprophylaxis program, none of the 101 breastfed infants and 9 formula-fed infants were positive for HBsAg [76]. An additional discussion of breastfeeding is found above. (See 'Breastfeeding' above.)

Prevention of mother-to-child transmission — Preventing mother-to-child transmission involves screening pregnant women, providing antiviral therapy to women with high HBV DNA levels, and administering passive-active immunization to newborns of mothers who are HBsAg positive (algorithm 1).

Maternal screening — All pregnant persons should be screened for HBV, preferably at the first prenatal visit [77]. Testing should be performed regardless of vaccination status and history of prior testing. Screening for hepatitis B will determine whether a person has current HBV infection and is at risk of transmitting HBV to the infant. This impacts the need for maternal antiviral therapy and post-exposure prophylaxis for the newborn. (See 'Maternal antiviral therapy to prevent transmission' below and 'Newborn immunization' below.)

The first time a pregnant person is screened they should be tested for HBsAg, anti-HBc, and anti-HBs. For subsequent pregnancies, HBsAg alone is sufficient.

- Pregnant persons who are HBsAg positive should have further testing to measure baseline HBeAg, hepatitis B e antibody (anti-HBe), HBV DNA, and aminotransferase levels. Those who have a high HBV DNA (ie, >2 x 10^5 international units/mL or >10^6 copies/mL), elevated aminotransferase levels, and/or a positive HBeAg should be referred to a hepatologist to see if early initiation of antiviral medications is needed (see 'Management considerations' above). In addition, the HBV status of any older children should be evaluated.

  Those with low HBV DNA levels in the first trimester should have repeat HBV viral load testing around weeks 26 to 28. If the levels have increased, antiviral therapy should be considered. (See 'Maternal antiviral therapy to prevent transmission' below.)

- Patients without evidence of prior HBV infection or exposure (negative for anti-HBs and anti-HBc) should be vaccinated [25]. In addition, those with risk factors for HBV (eg, injection drug use, having a sexual partner or household contact with chronic HBV, having had more than one sex partner in the previous six months, having been evaluated or treated for a STI) (table 3) should have HBsAg repeated late in pregnancy (approximately 28 weeks), if they are at risk of HBV infection.

- For those who have evidence of prior infection (HbsAg-negative, anti-HBc-positive, anti-HBs-positive) or immunity due to vaccination (HbsAg-negative, anti-HBc-negative, anti-HBs- positive), no further intervention is needed.

  However, a booster dose of vaccine is reasonable for patients who have isolated anti-HBc positive to see if anti-HBs titers can increase to >10 milli-international units/mL, although the clinical importance of this is unclear. (See "Hepatitis B virus: Screening and diagnosis in adults", section on 'Approach to screening and testing'.)

Women who are not tested prenatally should be tested at the time of admission for delivery [78].

Maternal antiviral therapy to prevent transmission

- **General approach** – For HbsAg-positive pregnant women who do not have indications for HBV therapy based on HBV parameters (see 'Management considerations' above), we recheck an HBV DNA level at 26 to 28 weeks gestation and recommend antiviral therapy at 28 weeks in those with HBV DNA levels >2 x 10^5 international units/mL or >10^6 copies/mL.

  Antiviral therapy should be given in addition to standard passive-active immunization of the infant to further reduce the risk of mother-to-child transmission (algorithm 1). The HBV DNA level threshold is based on the increased risk of transmission at these high viral loads despite postnatal vaccination. According to the World Health Organization (WHO), HbeAg may be used as an indicator for antiviral prophylaxis when testing for HBV DNA is not available [56]. (See 'HBV replicative status' above and 'HBV DNA level' above.)

  Although recommendations regarding when to start antiviral therapy have varied from week 24 to 32 [25,79,80], we start treatment around week 28 so there is sufficient time for the HBV viral load to decrease, even if the patient delivers early.

  For women who start treatment before 32 weeks, we typically check an HBV DNA level approximately four weeks after starting therapy. In our experience, patients who are taking their medications almost always have a drop by at least 2 to 3 log in their HBV DNA level. If the viral load has not dropped, we assess for potential barriers to adherence.

  The choice of agent and duration of therapy are discussed below.

  Our approach to antiviral therapy is consistent with recommendations by the American Association for the Study of Liver Disease; National Academies of Sciences, Engineering, and Medicine; the Advisory Committee on Immunization Practices; and the WHO [25,56,78,81].

- **Choice of agent** – For those who require treatment, we prefer tenofovir disoproxil fumarate (TDF) rather than other antiviral agents since resistance to TDF is rare. This is important since many of these young mothers may require antiviral treatment for their liver disease in the future. In addition, this agent appears to be safe for use in pregnancy and has been evaluated in several prospective clinical trials [82-84].

  A newer formulation of tenofovir, tenofovir alafenamide (TAF), is available. Although there is less bone and kidney toxicity with this agent compared with TDF, TAF has not been routinely recommended for treatment of HBV during pregnancy given the paucity of safety data.

However, there have been some observational studies evaluating the safety and efficacy of TAF for prevention of mother-to-child transmission. One prospective, observational study from China compared 116 mothers who received TAF to 116 mothers receiving TDF [26]. Treatment was initiated from gestational weeks 24 to 35 to delivery in mothers who had HBV DNA levels greater than 200,000 IU/mL. Infants received immunoprophylaxis and were followed for up to six months postpartum. The safety profile between the TDF and TAF groups were comparable with no birth defects seen in either group. The HBsAg positivity rate was zero percent at seven months in all 233 infants.

A smaller prospective study, also from China, evaluated the safety and efficacy of TAF in both early (<14 weeks of gestation) and middle (14 to 28 weeks of gestation) stages of pregnancy [27]. Infants were followed up to six months postpartum and all received immunoprophylaxis. Among the 98 mothers enrolled, TAF was initiated in 31 mothers in early pregnancy, while 57 mothers received TAF in middle pregnancy. At delivery, all mothers achieved complete HBV DNA suppression. Of the 98 infants born, none had congenital defects or malformations. There were no cases of mother-to-child transmission, and no severe adverse events were reported in either mothers or infants.

Although other agents (eg, lamivudine, telbivudine) also reduce mother-to-child transmission and appear to be safe when administered during pregnancy [82,85-88], they are associated with high rates of antiviral resistance. Lamivudine may be a reasonable alternative if cost is a barrier to obtaining antiviral therapy and treatment is going to be administered for a short duration (ie, ≤3 months). However, it is important that patients have not received lamivudine in the past, since such patients are at risk of having lamivudine-resistant virus.

Additional information on the safety of antiviral agents in pregnancy is found below. (See 'Safety of antiviral agents in pregnancy' below.)

- **Duration of antiviral therapy** – Women who start antiviral therapy during pregnancy for the sole purpose of preventing mother-to-child transmission may stop antiviral therapy immediately after delivery, especially if they want to breastfeed. Some experts prefer to continue treatment for 4 to 12 weeks after delivery, in part to reduce the risk of a flare postpartum [89]. However, in a prospective study where 91 women (101 pregnancies) received antiviral therapy to prevent transmission, extending antiviral therapy beyond delivery did not appear to reduce the frequency of HBV flares over a median of 48 weeks of follow-up [90].

Regardless of when antiviral therapy is discontinued, women should be monitored for a flare of their HBV disease by measuring the alanine aminotransferase (ALT) level every three months for six months after therapy has been stopped. For those that continue antiviral therapy after delivery (eg, for treatment of chronic HBV), the risks and benefits of breastfeeding must be discussed with the mother. (See 'Breastfeeding' above and 'Breastfeeding and transmission' above and "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy' and "Hepatitis B virus: Overview of management", section on 'Overview of antiviral agents'.)

- **Efficacy of antiviral therapy** – Data from clinical trials and prospective studies support the use of maternal antiviral therapy to reduce HBV transmission. A systematic review and meta-analysis of 129 studies found a protective effect of antiviral therapy, regardless of the agent used, with the odds ratio of HBV infection being 0.16 (95% CI 0.10-0.26) for TDF, 0.17 (95% CI 0.13-0.22) for lamivudine, and 0.20 (95% CI 0.08-0.13) for telbivudine [56]. In almost all the studies, infants received HBIG in addition to birth dose HBV vaccine. In an analysis of six studies that reported the risk of maternal HBV flare after discontinuation of TDF, the risk was similar between those who did and did not received TDF at a matched time-point (8 versus 6 percent, respectively).

  In a meta-analysis of 26 studies, which included 3622 pregnant women, antiviral therapy (in addition to passive and active immunization of the newborn) significantly reduced neonatal HBV transmission as evidenced by a reduced risk of infant HbsAg seropositivity (risk ratio 0.3; 95% CI 0.2-0.4) and a reduced risk of HBV DNA seropositivity (risk ratio 0.3; 95% CI 0.2-0.5) [83]. In addition, among mothers who received antiviral therapy and their newborns, there was no increased risk of adverse outcomes (eg, congenital malformations, prematurity, postpartum hemorrhage). However, there are concerns about the quality of the data in this analysis given the small numbers of events and the limited data on the safety of the antiviral agents in newborns.

  One of the key trials evaluating antiviral therapy was a randomized trial of 200 pregnant women from China who were HbeAg positive and had HBV DNA >2 x 10^5 international units/mL (median 10^8 international units/mL) at baseline received either TDF (300 mg) or placebo, starting at 30 to 32 weeks gestation and continuing 4 weeks postpartum [84]. All infants received standard immunoprophylaxis using HBIG and the hepatitis B vaccine. At postpartum week 28, the mother-to-child transmission rate was significantly lower for infants born to tenofovir-treated women compared with untreated women (5 versus 18 percent). Among the 92 mothers who received tenofovir and completed the trial, there was no transmission of HBV. In addition, no significant differences in the rate of birth defects

between babies born to treated and untreated mothers (2.1 versus 1.1 percent) were noted. After treatment was discontinued, more of the mothers who received tenofovir had elevations in their alanine aminotransferase levels, but none of the mothers had severe flares or hepatic decompensation.

The efficacy of tenofovir in reducing mother-to-child transmission was also demonstrated in a prospective study of 118 pregnant women who had an HBV DNA $\geq 10^{7.5}$ international units/mL and were positive for HbsAg and HbeAg [82]. Women received tenofovir (300 mg daily), which was initiated at week 30 to 32 of gestation, or no antiviral therapy, and treatment was continued for one month postpartum. All infants received passive and active immunization. Newborns born to mothers who received tenofovir had significantly lower rates of HbsAg positivity at six months (1.5 versus 10.7 percent).

Conflicting results were found in a randomized trial in Thailand that evaluated the use of maternal TDF in 331 pregnant women with chronic HBV and a median HBV viral load of 10^8 international units/mL. In this trial, mothers initiated TDF or placebo at week 28 and continued therapy for two months postpartum [91]. All newborns received HBIG plus hepatitis B vaccine at birth, and then four additional doses of hepatitis B vaccine at one, two, four, and six months. Among those women who completed the study (147 in each arm), there was no difference in rates of transmission (0 versus 2 percent, not significant). Approximately 10 percent of patients in each group were lost to follow-up; however, similar results were obtained if last available infection status was imputed or analysis was performed with missing data imputed as infected.

Although TDF did not demonstrate a clear benefit in this trial, these findings do not alter our approach to maternal antiviral therapy since the generalizability is limited. As an example, the adherence to the protocol for infant immunoprophylaxis in this trial may not be replicable in other settings. HBIG and birth-dose vaccine are not available in many countries despite recommendations from the WHO [92]. Even in countries with birth-dose HBV vaccination programs, such as the United States, the recommended timing of HBV vaccine is within 12 hours of birth [78], and only 71.1 percent of infants receive birth-dose HBV vaccine by three days of life [93]. In addition, infants in this study received four doses of HBV vaccine before assessment for HBV infection at six months, whereas most guidelines recommend only two to three doses before six months (table 4A). The results of this study do not refute the current recommendation to administer antiviral therapy to highly viremic mothers, but suggest that further investigation of postexposure immunization regimens may be warranted.

Newborn immunization — Newborns of mothers who test positive for HbsAg should receive passive-active immunization, with the first dose of the hepatitis B vaccine series and one dose of HBIG administered within 12 hours of delivery at different sites (table 4A-B). Infants should then complete the hepatitis B vaccine series. A more detailed discussion of HBV immunization in infants born to HbsAg-positive mothers is found elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'HBsAg-positive mother or mother with other evidence of HBV infection'.)

The importance of the timing of the birth-dose HBV vaccine was highlighted in a study in Cameroon of 1800 infants of HBsAg-positive mothers who received birth-dose vaccine and the three-dose pentavalent vaccine but no HBIG and none of the mothers received antiviral therapy [94]. The prevalence of HBsAg among the children who received birth dose vaccine in less than 24 hours was 5.6 percent versus 16.7 percent in those who received the birth dose vaccine 48 to 96 hours after birth. One limitation of this study was the varying time when the children were tested for HBsAg; some children were tested after the age of three years, therefore, horizontal transmission could not be ruled out.

To eliminate viral hepatitis B by 2030, the World Health Assembly adopted the Global Health Sector Strategy (GHSS) on viral hepatitis in 2016 [40]. Programmatic targets for vaccination are ≥90 percent coverage of timely hepatitis B birth dose and three doses of HBV vaccine (HepB3). By December 2020, 98 percent of WHO member states had introduced universal infant hepatitis B vaccination, and 57 percent of countries provided HepB-birth-dose vaccine to all newborns [95]. However, only 54 percent had timely administration of the birth dose, and only 52 percent of countries had ≥90 percent HepB3 coverage. There was even a small decline in hepatitis B vaccine coverage in 2020, particularly HepB3, attributed to disruption in service caused by the COVID-19 pandemic.

There was a marked difference in hepatitis B vaccination coverage in different regions of the world, with the lowest in the African region and the highest in the Western Pacific region (16 percent versus 81 percent for HepB-BD, and 73 percent versus 94 percent for HepB3). These findings highlight the need to identify and overcome barriers to hepatitis B vaccination in the African region, where prevalence of hepatitis B remains high.

SAFETY OF ANTIVIRAL AGENTS IN PREGNANCY

Overview — Therapeutic options for the treatment of chronic hepatitis B virus (HBV) in nonpregnant women include oral nucleos(t)ide analogues and pegylated interferon. However, in pregnant women, interferon should be **avoided** because of concerns of pregnancy loss [96].

(See "Hepatitis B virus: Overview of management", section on 'Antiviral therapy' and 'Other potential adverse events' below.)

Certain nucleos(t)ides appear safe (eg, tenofovir disoproxil fumarate [TDF]), although none of the HBV agents are approved by the US Food and Drug Administration (FDA) for use in pregnancy since there are no large studies that have addressed the safety of antiviral therapy in HBV-monoinfected women during pregnancy. Most safety data are from HIV-infected patients where combination antiviral regimens are used [89]. (See "Safety and dosing of antiretroviral medications in pregnancy", section on 'Lamivudine' and "Safety and dosing of antiretroviral medications in pregnancy", section on 'Tenofovir'.)

Risk of teratogenicity — There are limited human data available on the risk of teratogenicity of antiviral agents used to treat HBV [82,83,85-88,97]. Available animal and human data have found no evidence of teratogenicity for TDF and telbivudine. Human studies also support the safety of lamivudine in pregnancy, although adverse events were observed in some animal studies. There are less safety data for tenofovir alafenamide, entecavir, or adefovir in pregnancy; thus, the risk of teratogenicity cannot be ruled out.

In 1989, The Antiretroviral Pregnancy Registry was established to evaluate the potential teratogenic effects of HIV agents. In 2003, the registry began collecting data on exposure to HBV agents as well. Information provided to the registry originates from clinical studies and retrospective reports of antiviral exposure. Data from the registry suggest the percentage of infants with birth defects who were born to HIV- and/or HBV-infected women exposed to antiviral agents was no greater than the 3 percent rate of birth defects found in the general population in the United States [98,99]. As examples:

- Lamivudine – 3.1 percent (170 of 5510) of infants born to mothers who took lamivudine during the first trimester developed birth defects, and 2.9 percent (218 of 7513) of infants born to mothers who took lamivudine during the second and third trimesters of pregnancy developed birth defects.

- Tenofovir disoproxil fumarate – 2.5 percent (115 of 4657) of infants born to mothers who took tenofovir disoproxil fumarate (TDF) during the first trimester developed birth defects, and 2.6 percent (51 of 1983) of infants born to mothers who took TDF during the second and third trimester of pregnancy developed birth defects.

- Tenofovir alafenamide – 3.5 percent (24 of 684) of infants born to mothers who took tenofovir alafenamide (TAF) during the first trimester developed birth defects, and 3.3 percent (5 of 152) of infants born to mothers who took TAF during the second/third trimester developed birth defects.

- **Other agents** – For entecavir, only 82 infants were reported to be exposed during the first trimester, only two during the second, and none during the third trimester, with only two birth defects reported in the first-trimester group. For adefovir, only 82 infants were reported to be exposed in the first trimester, four during the second/third trimester, with no reports of birth defects. There were a total of 253 exposures to telbivudine and three reports of birth defects in the first trimester; in addition, telbivudine had been studied and reported to be safe in several clinical trials [85,86].

The registry has also collected data on HBV-monoinfected patients. Through January 2022, the registry included data on 864 HBV-monoinfected pregnancies. Twelve birth defect cases were reported among 801 live births. There was no pattern among the types of birth defects reported [99].

There are important limitations to these observations. The registry depends upon voluntary reporting, and the information is not verified. Long-term follow-up is limited, and there are no efforts to confirm the diagnosis of birth defects. Furthermore, data are available for birth defects among live births, but there are no data on miscarriages or subsequent developmental delays. Much of the clinical data have been on lamivudine and TDF because these drugs are also used for treatment of HIV infection.

Other potential adverse events — A number of adverse events of nucleos(t)ide analogues have been described, including mitochondrial damage, lactic acidosis, acute fatty liver, and possibly bone abnormalities.

- **Symptomatic lactic acidosis** – Symptomatic lactic acidosis has been reported in infants born to HIV-infected mothers who were exposed to certain antiretroviral agents (which included nucleos(t)ide analogues) in utero, but it has not been observed in infants exposed to HBV antiviral agents in utero. Thus, monitoring for lactic acidosis in the infant is not necessary if the mother received HBV antiviral agents only. (See "Safety and dosing of antiretroviral medications in pregnancy", section on 'Mitochondrial toxicity'.)

- **Bone abnormalities** – TDF is associated with decreased bone mineral density, which usually stabilizes with continued use. There have been concerns about the effect of maternal TDF on fetal growth and development; however, studies evaluating infants born to women who received TDF during pregnancy are generally reassuring [100-103]. As an example, in the randomized trial described above [91], in which women with HBV monoinfection received TDF or placebo from 28 weeks gestational age to two months postpartum, there was no effect on maternal or infant bone density one year after delivery in the 140 mothers and 137 infants who were evaluated [103]. Although another study

found that infants born to HIV-infected mothers who were exposed to TDF had a 12 percent lower bone mineral content in the first month of life compared with those who had no tenofovir exposure [104], the clinical and long-term significance of these findings are uncertain.

A newer formulation of tenofovir, tenofovir alafenamide, may have less bone toxicity compared with TDF, but we do **not** use tenofovir alafenamide at this time during pregnancy given the lack of sufficient safety data. (See 'Maternal antiviral therapy to prevent transmission' above.)

- **Effects on growth** – Studies mainly in the HIV population have not revealed an effect of TDF on birth weight, although there are conflicting results regarding the effect on head circumference and growth (eg, length) [101,102,105,106]. However, in a study that evaluated 646 HIV-infected pregnant women receiving TDF, there was no association between duration of in utero tenofovir exposure and fetal long bone growth, which was assessed using ultrasound [107].

- **Pregnancy loss** – Interferon has been associated with abortifacient effects in rhesus monkeys [96]. There are no such reports in humans [108]; however, since data are limited, all women receiving interferon therapy must use birth control, and interferon must be stopped if women become pregnant. (See 'Patients who are pregnant' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis B vaccination" and "Society guideline links: Management of hepatitis B".)

SUMMARY AND RECOMMENDATIONS

- **Considerations for management of HBV in pregnancy** – Hepatitis B virus (HBV) infection during pregnancy presents with unique management issues for both the mother and fetus. These include the effects of HBV on maternal and fetal health, the effects of pregnancy on the course of HBV infection, treatment of HBV during pregnancy, and prevention of mother-to-child transmission. (See 'Introduction' above.)

- **Acute HBV in pregnancy** – Acute HBV infection during pregnancy is usually not severe and is not associated with increased mortality or teratogenicity. Treatment is mainly

supportive. However, acute HBV has been associated with mother-to-child transmission. If the mother remains hepatitis B surface antigen (HBsAg) positive or has a detectable HBV DNA, the infant should receive hepatitis B immune globulin (HBIG) in addition to routine hepatitis B vaccination. Antiviral therapy for the mother may also be indicated to reduce the risk of transmission (algorithm 1). (See 'Acute Hepatitis B virus infection' above and 'Prevention of mother-to-child transmission' above.)

- **Chronic HBV in pregnancy** – Pregnancy is generally well tolerated by women with chronic HBV who do not have advanced liver disease. However, HBsAg-positive mothers should be monitored closely during pregnancy and the postpartum period, since such women are at risk of developing a hepatitis flare. (See 'Impact of pregnancy on the natural history of chronic HBV' above.)

  For mothers with chronic HBV, the impact of HBV infection on newborns is not well defined, and data are conflicting. However, women with cirrhosis are at significant risk for perinatal complications and poor maternal and fetal outcomes, including intrauterine growth restriction, intrauterine infection, premature delivery, and intrauterine fetal demise. (See 'Effect of chronic HBV on pregnancy outcomes' above.)

- **Preventing mother to child transmission** – The infection rate among infants born to HBsAg-positive mothers who do not receive any form of neonatal prophylaxis is as high as 90 percent. However, administering HBIG and hepatitis B vaccine to infants at delivery can reduce transmission by at least 95 percent. The most important risk factors for transmission, despite prophylaxis, appear to be a positive hepatitis B e antigen (HBeAg) in the mother and a high maternal HBV viral load (>200,000 international units/mL). (See 'Risk of transmission' above and 'Risk factors for transmission' above.)

  - **Maternal screening** – For persons who are pregnant, we recommend screening for HBV (**Grade 1B**). The first time a person is screened they should be tested for HBsAg, anti-HBc, and anti-HBs. For subsequent pregnancies, HBsAg alone is sufficient. (See 'Maternal screening' above.)

    Screening should ideally be performed at the first prenatal visit. HBsAg testing should be repeated late in pregnancy in those without evidence of infection or immunity if they are at high risk for HBV infection (table 3).

  - **Management of newborns** – Newborns of HBsAg-positive mothers should receive passive-active immunization (HBIG and hepatitis B vaccine) within 12 hours of delivery and then complete the hepatitis B vaccine series (algorithm 1). (See 'Newborn

immunization' above and "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Routine infant immunization'.)

Infants who received HBIG and the first dose of hepatitis B vaccine at birth can be breastfed. It is important that such infants complete the course of vaccination. However, if maternal antiviral therapy is continued after delivery, low levels of tenofovir are detected in maternal breastmilk. Although this is unlikely to have any biological effects on the nursing infant, data are limited and the decision to breastfeed should be based upon patient preference. (See 'Breastfeeding and transmission' above and 'Breastfeeding' above.)

- **Role of maternal antiviral therapy** – In addition to passive-active immunization of newborns, antiviral therapy for the mother may reduce the risk of mother-to-child transmission. The importance of antiviral therapy increases with increasing viral load. For mothers not already on treatment, we test HBV DNA level at 26 to 28 weeks (algorithm 1).

  For pregnant women with an HBV viral load >2 x 10^5 international units/mL (>10^6 copies/mL), we recommend antiviral therapy (**Grade 1B**). We initiate antiviral therapy at 28 weeks gestation. We prefer tenofovir disoproxil fumarate (TDF) since it appears safe in pregnancy, and the risk of drug resistance is low. Patients should be monitored for a flare if antiviral therapy is discontinued after delivery. (See 'Prevention of mother-to-child transmission' above and 'Safety of antiviral agents in pregnancy' above.)

REFERENCES

1. Sookoian S. Liver disease during pregnancy: acute viral hepatitis. Ann Hepatol 2006; 5:231.
2. Hieber JP, Dalton D, Shorey J, Combes B. Hepatitis and pregnancy. J Pediatr 1977; 91:545.
3. Jonas MM. Hepatitis B and pregnancy: an underestimated issue. Liver Int 2009; 29 Suppl 1:133.
4. Degertekin B, Lok AS. Indications for therapy in hepatitis B. Hepatology 2009; 49:S129.
5. Potthoff A, Rifai K, Wedemeyer H, et al. Successful treatment of fulminant hepatitis B during pregnancy. Z Gastroenterol 2009; 47:667.
6. Rawal BK, Parida S, Watkins RP, et al. Symptomatic reactivation of hepatitis B in pregnancy. Lancet 1991; 337:364.

7. Giles M, Visvanathan K, Lewin S, et al. Clinical and virological predictors of hepatic flares in pregnant women with chronic hepatitis B. Gut 2015; 64:1810.
8. Lin HH, Wu WY, Kao JH, Chen DS. Hepatitis B post-partum e antigen clearance in hepatitis B carrier mothers: Correlation with viral characteristics. J Gastroenterol Hepatol 2006; 21:605.
9. ter Borg MJ, Leemans WF, de Man RA, Janssen HL. Exacerbation of chronic hepatitis B infection after delivery. J Viral Hepat 2008; 15:37.
10. Yang YB, Li XM, Shi ZJ, Ma L. Pregnant woman with fulminant hepatic failure caused by hepatitis B virus infection: a case report. World J Gastroenterol 2004; 10:2305.
11. Kushner T, Shaw PA, Kalra A, et al. Incidence, determinants and outcomes of pregnancy-associated hepatitis B flares: A regional hospital-based cohort study. Liver Int 2018; 38:813.
12. Nguyen G, Garcia RT, Nguyen N, et al. Clinical course of hepatitis B virus infection during pregnancy. Aliment Pharmacol Ther 2009; 29:755.
13. Tan HH, Lui HF, Chow WC. Chronic hepatitis B virus (HBV) infection in pregnancy. Hepatol Int 2008; 2:370.
14. Söderström A, Norkrans G, Lindh M. Hepatitis B virus DNA during pregnancy and post partum: aspects on vertical transmission. Scand J Infect Dis 2003; 35:814.
15. Lao TT, Chan BC, Leung WC, et al. Maternal hepatitis B infection and gestational diabetes mellitus. J Hepatol 2007; 47:46.
16. Lao TT, Tse KY, Chan LY, et al. HBsAg carrier status and the association between gestational diabetes with increased serum ferritin concentration in Chinese women. Diabetes Care 2003; 26:3011.
17. Lobstein S, Faber R, Tillmann HL. Prevalence of hepatitis B among pregnant women and its impact on pregnancy and newborn complications at a tertiary hospital in the eastern part of Germany. Digestion 2011; 83:76.
18. Connell LE, Salihu HM, Salemi JL, et al. Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. Liver Int 2011; 31:1163.
19. Wong S, Chan LY, Yu V, Ho L. Hepatitis B carrier and perinatal outcome in singleton pregnancy. Am J Perinatol 1999; 16:485.
20. Tse KY, Ho LF, Lao T. The impact of maternal HBsAg carrier status on pregnancy outcomes: a case-control study. J Hepatol 2005; 43:771.
21. Reddick KL, Jhaveri R, Gandhi M, et al. Pregnancy outcomes associated with viral hepatitis. J Viral Hepat 2011; 18:e394.
22. Safir A, Levy A, Sikuler E, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier

status as an independent risk factor for adverse perinatal outcome. Liver Int 2010; 30:765.

23. Society for Maternal-Fetal Medicine (SMFM), Dionne-Odom J, Tita AT, Silverman NS. #38: Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission. Am J Obstet Gynecol 2016; 214:6.
24. Shaheen AA, Myers RP. The outcomes of pregnancy in patients with cirrhosis: a population-based study. Liver Int 2010; 30:275.
25. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.
26. Zeng QL, Yu ZJ, Ji F, et al. Tenofovir Alafenamide to Prevent Perinatal Hepatitis B Transmission: A Multicenter, Prospective, Observational Study. Clin Infect Dis 2021; 73:e3324.
27. Chen R, Zou J, Long L, et al. Safety and Efficacy of Tenofovir Alafenamide Fumarate in Early-Middle Pregnancy for Mothers With Chronic Hepatitis B. Front Med (Lausanne) 2021; 8:796901.
28. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv (Accessed on April 17, 2023).
29. American Academy of Pediatrics. Hepatitis B. In: Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Elk Grove Village, IL 2015. p.400.
30. Cundy KC, Sueoka C, Lynch GR, et al. Pharmacokinetics and bioavailability of the anti-human immunodeficiency virus nucleotide analog 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. Antimicrob Agents Chemother 1998; 42:687.
31. Van Rompay KK, Hamilton M, Kearney B, Bischofberger N. Pharmacokinetics of tenofovir in breast milk of lactating rhesus macaques. Antimicrob Agents Chemother 2005; 49:2093.
32. Benaboud S, Pruvost A, Coffie PA, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob Agents Chemother 2011; 55:1315.
33. Ehrhardt S, Xie C, Guo N, et al. Breastfeeding while taking lamivudine or tenofovir disoproxil fumarate: a review of the evidence. Clin Infect Dis 2015; 60:275.
34. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing

African mother-infant pairs. J Antimicrob Chemother 2018; 73:1013.

35. Erturk US, Mete B, Ozaras R, et al. Plasma and Breast Milk Pharmacokinetics of Tenofovir Disoproxil Fumarate in Nursing Mother with Chronic Hepatitis B-Infant Pairs. Antimicrob Agents Chemother 2021; 65:e0111021.
36. Gouraud A, Millaret A, Bernard N, et al. Tenofovir exposure through breast feeding: Serum concentrations in neonates and clinical follow-up. Fundam Clin Pharmacol. 2012;26 (Suppl 1):9
37. Pan CQ, Mi LJ, Bunchorntavakul C, et al. Tenofovir disoproxil fumarate for prevention of vertical transmission of hepatitis B virus infection by highly viremic pregnant women: a case series. Dig Dis Sci 2012; 57:2423.
38. Ganne-Carrie N, Causse X, Zarski JP et al. Efficacy and safety results of tenofovir DF (TDF) tre atment from the first trimester in HBV pregnant women in real-life clinical practice. Hepatol ogy. 2013;58 (Suppl 1):664A-5A
39. Lactmed. Tenofovir. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~SOkg2H:1.
40. World Health Organization. Global health sector strategy on viral hepatitis, 2016–2021: tow ards ending viral hepatitis. Geneva, Switzerland: World Health Organization; 2016. https://a pps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf (Accessed on March 15, 2023).
41. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975; 292:771.
42. Schillie S, Walker T, Veselsky S, et al. Outcomes of infants born to women infected with hepatitis B. Pediatrics 2015; 135:e1141.
43. Xu DZ, Yan YP, Choi BC, et al. Risk factors and mechanism of transplacental transmission of hepatitis B virus: a case-control study. J Med Virol 2002; 67:20.
44. Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus transmission in the United States. Prevention by passive-active immunization. JAMA 1985; 253:1740.
45. Chen HL, Lin LH, Hu FC, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology 2012; 142:773.
46. Thompson ND, Perz JF, Moorman AC, Holmberg SD. Nonhospital health care-associated hepatitis B and C virus transmission: United States, 1998-2008. Ann Intern Med 2009; 150:33.
47. Guidelines for Perinatal Care. In: American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 4th ed, Washington, DC 1997. p.286.

48. Soldan K, Ramsay M, Collins M. Acute hepatitis B infection associated with blood transfusion in England and Wales, 1991-7: review of database. BMJ 1999; 318:95.

49. Zou H, Chen Y, Duan Z, et al. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012; 19:e18.

50. Miyakawa M, Yoshida LM, Nguyen HT, et al. Hepatitis B virus infection among pregnant mothers and children after the introduction of the universal vaccination program in Central Vietnam. Sci Rep 2021; 11:8676.

51. Burk RD, Hwang LY, Ho GY, et al. Outcome of perinatal hepatitis B virus exposure is dependent on maternal virus load. J Infect Dis 1994; 170:1418.

52. Li XM, Shi MF, Yang YB, et al. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. World J Gastroenterol 2004; 10:3215.

53. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009; 190:489.

54. Wen WH, Chang MH, Zhao LL, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol 2013; 59:24.

55. Kubo A, Shlager L, Marks AR, et al. Prevention of vertical transmission of hepatitis B: an observational study. Ann Intern Med 2014; 160:828.

56. World Health Organization. Prevention of mother-to-child transmission of hepatitis B virus: Guidelines on antiviral prophylaxis in pregnancy. July 2020. https://apps.who.int/iris/bitstream/handle/10665/333391/9789240002708-eng.pdf?sequence=1&isAllowed=y (Accessed on September 03, 2020).

57. Lin HH, Lee TY, Chen DS, et al. Transplacental leakage of HBeAg-positive maternal blood as the most likely route in causing intrauterine infection with hepatitis B virus. J Pediatr 1987; 111:877.

58. Ohto H, Lin HH, Kawana T, et al. Intrauterine transmission of hepatitis B virus is closely related to placental leakage. J Med Virol 1987; 21:1.

59. Bai H, Zhang L, Ma L, et al. Relationship of hepatitis B virus infection of placental barrier and hepatitis B virus intra-uterine transmission mechanism. World J Gastroenterol 2007; 13:3625.

60. Zhang SL, Yue YF, Bai GQ, et al. Mechanism of intrauterine infection of hepatitis B virus. World J Gastroenterol 2004; 10:437.

61. Ijaz S, Derrick J, Shute J, et al. Mother to Infant Transmission of Hepatitis B Virus in the Face of Neonatal Immunization Is Not Necessarily Primary Vaccine Failure. Clin Infect Dis 2022;

74:1151.

62. López M, Coll O. Chronic viral infections and invasive procedures: risk of vertical transmission and current recommendations. Fetal Diagn Ther 2010; 28:1.
63. Towers CV, Asrat T, Rumney P. The presence of hepatitis B surface antigen and deoxyribonucleic acid in amniotic fluid and cord blood. Am J Obstet Gynecol 2001; 184:1514.
64. Yi W, Pan CQ, Hao J, et al. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol 2014; 60:523.
65. Ko TM, Tseng LH, Chang MH, et al. Amniocentesis in mothers who are hepatitis B virus carriers does not expose the infant to an increased risk of hepatitis B virus infection. Arch Gynecol Obstet 1994; 255:25.
66. Han Z, Zhang Y, Bai X, et al. Mother-to-child transmission of hepatitis B virus after amniocentesis: A retrospective matched cohort study. Prenat Diagn 2019; 39:431.
67. Chen LZ, Zhou WQ, Zhao SS, et al. A nested case-control study of maternal-neonatal transmission of hepatitis B virus in a Chinese population. World J Gastroenterol 2011; 17:3640.
68. Song YM, Sung J, Yang S, et al. Factors associated with immunoprophylaxis failure against vertical transmission of hepatitis B virus. Eur J Pediatr 2007; 166:813.
69. Wang J, Zhu Q, Zhang X. Effect of delivery mode on maternal-infant transmission of hepatitis B virus by immunoprophylaxis. Chin Med J (Engl) 2002; 115:1510.
70. Yang J, Zeng XM, Men YL, Zhao LS. Elective caesarean section versus vaginal delivery for preventing mother to child transmission of hepatitis B virus--a systematic review. Virol J 2008; 5:100.
71. Chang MS, Gavini S, Andrade PC, McNabb-Baltar J. Caesarean section to prevent transmission of hepatitis B: a meta-analysis. Can J Gastroenterol Hepatol 2014; 28:439.
72. Pan YC, Jia ZF, Wang YQ, et al. The role of caesarean section and nonbreastfeeding in preventing mother-to-child transmission of hepatitis B virus in HBsAg-and HBeAg-positive mothers: results from a prospective cohort study and a meta-analysis. J Viral Hepat 2020; 27:1032.
73. Levy MT, Terrault NA. Caesarean section or non-breastfeeding for prevention of MTCT-beware of sending the wrong message. J Viral Hepat 2021; 28:575.
74. Tran TT. Hepatitis B in Pregnancy. Clin Infect Dis 2016; 62 Suppl 4:S314.
75. Beasley RP, Stevens CE, Shiao IS, Meng HC. Evidence against breast-feeding as a mechanism for vertical transmission of hepatitis B. Lancet 1975; 2:740.

76. Hill JB, Sheffield JS, Kim MJ, et al. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. Obstet Gynecol 2002; 99:1049.
77. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep 2023; 72:1.
78. Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67:1.
79. Kumar M, Abbas Z, Azami M, et al. Asian Pacific association for the study of liver (APASL) guidelines: hepatitis B virus in pregnancy. Hepatol Int 2022; 16:211.
80. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67:370.
81. National Academies of Sciences, Engineering, and Medicine. A national strategy for the eli mination of hepatitis B and C. Washington, DC. The National Academies Press, 2017.
82. Chen HL, Lee CN, Chang CH, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology 2015; 62:375.
83. Brown RS Jr, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. Hepatology 2016; 63:319.
84. Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016; 374:2324.
85. Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol 2011; 55:1215.
86. Pan CQ, Han GR, Jiang HX, et al. Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. Clin Gastroenterol Hepatol 2012; 10:520.
87. Shi Z, Yang Y, Ma L, et al. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstet Gynecol 2010; 116:147.
88. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat 2009; 16:94.
89. Visvanathan K, Dusheiko G, Giles M, et al. Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New

Zealand key opinion leaders. Gut 2016; 65:340.

90. Nguyen V, Tan PK, Greenup AJ, et al. Anti-viral therapy for prevention of perinatal HBV transmission: extending therapy beyond birth does not protect against post-partum flare. Aliment Pharmacol Ther 2014; 39:1225.
91. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus Placebo to Prevent Perinatal Transmission of Hepatitis B. N Engl J Med 2018; 378:911.
92. World Health Organization. Immunization, Vaccines and Biologicals: Data, statistics and graphics. http://www.who.int/immunization/monitoring_surveillance/data/en/ (Accessed on March 19, 2018).
93. Hill HA, Elam-Evans LD, Yankey D, et al. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2016. MMWR Morb Mortal Wkly Rep 2017; 66:1171.
94. Shimakawa Y, Veillon P, Birguel J, et al. Residual risk of mother-to-child transmission of hepatitis B virus infection despite timely birth-dose vaccination in Cameroon (ANRS 12303): a single-centre, longitudinal observational study. Lancet Glob Health 2022; 10:e521.
95. Khetsuriani N, Lesi O, Desai S, et al. Progress Toward the Elimination of Mother-to-Child Transmission of Hepatitis B Virus - Worldwide, 2016-2021. MMWR Morb Mortal Wkly Rep 2022; 71:958.
96. Intron-A [package insert]. Kenilworth, NJ. Schering Corporation; 1994.
97. Pan CQ, Duan ZP, Dai E, et al. Tenofovir disoproxil fumarate (TDF) reduces perinatal transmission of hepatitis B virus in highly viremic mothers: A multi-center, prospective, randomized and controlled study. Presented at the AASLD Liver Meeting 2015. San Francisco, 2015.
98. Hoyert DL, Mathews TJ, Menacker F, et al. Annual summary of vital statistics: 2004. Pediatrics 2006; 117:168.
99. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2018. Wilmington, NC: Registry Coordinating Center; 2017. Available from URL: www.APRegistry.com. (Accessed on July 13, 2021).
100. Gill US, et al. Factors determining bone mineral density loss in chronic hepatitis B patients: is tenofovir disoproxil fumarate the main culprit? Gut 2011; 60:A230.
101. Gibb DM, Kizito H, Russell EC, et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. PLoS Med 2012; 9:e1001217.
102. Wang L, Kourtis AP, Ellington S, et al. Safety of tenofovir during pregnancy for the mother and fetus: a systematic review. Clin Infect Dis 2013; 57:1773.

103. Salvadori N, Fan B, Teeyasoontranon W, et al. Maternal and Infant Bone Mineral Density 1 Year After Delivery in a Randomized, Controlled Trial of Maternal Tenofovir Disoproxil Fumarate to Prevent Mother-to-child Transmission of Hepatitis B Virus. Clin Infect Dis 2019; 69:144.

104. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. Clin Infect Dis 2015; 61:996.

105. Viganò A, Mora S, Giacomet V, et al. In utero exposure to tenofovir disoproxil fumarate does not impair growth and bone health in HIV-uninfected children born to HIV-infected mothers. Antivir Ther 2011; 16:1259.

106. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. AIDS 2012; 26:1151.

107. Jao J, Abrams EJ, Phillips T, et al. In Utero Tenofovir Exposure Is not Associated With Fetal Long Bone Growth. Clin Infect Dis 2016; 62:1604.

108. Trotter JF, Zygmunt AJ. Conception and pregnancy during interferon-alpha therapy for chronic hepatitis C. J Clin Gastroenterol 2001; 32:76.

Topic 83476 Version 28.0

GRAPHICS

Recommendations for initial treatment of chronic hepatitis B in nonpregnant adults

HBeAg	HBV DNA (PCR)	ALT	Treatment strategy
Patients without cirrhosis*			
+	>20,000 international units/mL	≤2 x ULN[¶]	Treatment is not recommended, because current treatment has low efficacy in inducing HBeAg seroconversion. Treatment may be considered in older patients (>40 years) and in those with family history of HCC.
			Patients should be monitored[Δ] and treatment considered if ALT becomes elevated >2 x ULN, liver biopsy shows moderate/severe inflammation or fibrosis[◇] (eg, METAVIR score ≥F2), and/or noninvasive testing suggests moderate/severe fibrosis.
+	>20,000 international units/mL	>2 x ULN[¶]	Observe for 3 to 6 months if compensated and treat if no spontaneous HBeAg loss.
			Immediate treatment if severe hepatitis flare (eg, icteric or clinical decompensation).
			ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – Seroconversion from HBeAg to anti-HBe.[‡]
			Duration of therapy:
			▪ PegIFN alfa: 48 weeks.
			▪ ETV, TAF, or TDF: Continue for at least 12 months after HBeAg seroconversion.
–	>2000 international units/mL	>2 x ULN[¶] OR 1 to 2 x ULN[¶] if liver biopsy shows moderate/severe necroinflammation or significant	ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – HBsAg loss.
			Duration of therapy:

		fibrosis◇ (eg, METAVIR score ≥F2) or non-invasive testing shows significant fibrosis	▪ PegIFN alfa: One year. ▪ ETV, TAF, or TDF: Several years or indefinite.†
–	≤2000 international units/mL	≤ULN¶	Monitor and treat if HBV DNA and ALT increase as described above.
Patients with cirrhosis*			
+/–	Detectable	Any ALT	Compensated: ▪ HBV DNA >2000 international units/mL – Treat with ETV, TAF, or TDF.§¥ Treatment should be continued indefinitely.** ▪ HBV DNA <2000 international units/mL – Consider treatment particularly if ALT elevated; close monitoring if treatment is not initiated. Decompensated: ▪ Treat immediately, regardless of ALT or HBV DNA levels. ETV preferred.§¥ TDF may be used with close monitoring of renal function. Refer for liver transplant.
+/–	Undetectable	Any ALT	Compensated: Observe, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis if HBV DNA remains undetectable. Decompensated: Refer for liver transplant, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis.

ALT: alanine aminotransferase; anti-HBe: antibody to hepatitis B e antigen; ETV: entecavir; HBeAg: Hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; PegIFN alfa: pegylated interferon alfa; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

* Based upon findings on noninvasive testing or liver biopsy performed during the initial evaluation. Patients with advanced fibrosis determined by noninvasive methods should be evaluated using a second method, and if results are concordant, consider managing the same way as patients with cirrhosis.

¶ The American Association for the Study of Liver Diseases (AASLD) recommends using an ALT >35 U/L for men and >25 U/L for women as the upper limit of normal (ULN) rather than local laboratory values.

Δ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of monitoring.

◇ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of indications for biopsy.

§ Adefovir, lamivudine, and telbivudine are not recommended due to a high rate of resistance after the first year and/or weak antiviral activity.

¥ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of which agent to use.

‡ Up to 50% of patients who achieve HBeAg seroconversion can experience a virologic relapse after discontinuing treatment with oral agents. Thus, some providers prefer to treat until HBsAg-loss.

† For most patients, antiviral therapy should be continued indefinitely. However, treatment discontinuation may be considered in persons without cirrhosis who have demonstrated loss of HBsAg and in selected patients who have had undetectable serum HBV DNA for >3 years and agree to close monitoring after stopping treatment. Persons who stop antiviral therapy should be monitored every month for the first six months. Refer to the UpToDate topic on management of hepatitis B virus infection for a detailed discussion of the risks and benefits of stopping antiviral therapy in this setting.

** This includes HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on therapy.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

Graphic 58520 Version 22.0

Diagnostic tests to determine phase of acute or chronic hepatitis B virus infection[1]

HBsAg	HBeAg	IgM anti-HBc	Total anti-HBc*	Anti-HBs	Anti-HBe	HBV DNA	ALT¶	Interpretati
Acute HBV infection								
+	+	+	±			+++	Elevated	Early phase
		+	±			+	Elevated	Window phase
			+	+	+	±	Normal	Recovery phas
Chronic HBV infection (HBsAg-positive for >6 months)								
+	+		+	-	-	+++ (Serum HBV typically >1 million international units/mL)	Normal or mildly elevated	Immune-tolera phase[Δ]
+	+		+	-	-	+++ (Serum HBV >20,000 international units/mL)	Persistently elevated	Immune-active HBeAg-positive
+	-		+	-	+	++ (Serum HBV >2000 international units/mL)	Elevated	Immune-active HBeAg-negativ
+	-		+		+	- to ++ (Serum HBV ≤2000 international units/mL)	Normal or mildly elevated	Inactive chroni HBV[§]
-	-		± (generally +)	±	±	+ in liver; - to + in serum	Normal	Occult HBV

ALT: alanine aminotransferase; anti-HBc: antibody to hepatitis B core antigen; anti-HBe: antibody to hepatitis B e antigen; anti-HBs: antibody to hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

* This test is typically ordered as total anti-HBc, which includes IgM and IgG.

¶ The upper limits of normal for ALT in healthy adults are reported to be 29 to 33 units/L for males and 19 to 25 units/L for females. For healthy children after infancy, the upper limits of normal are 25 to 38 units/L and 22 to 31 units/L for boys and girls, respectively.

Δ For patients with immune-tolerant chronic hepatitis B, liver biopsy or noninvasive tests show no fibrosis and minimal inflammation. This is the initial phase seen in patients with perinatally acquired HBV infection.

◇ For patients with immune active chronic hepatitis B, liver biopsy or noninvasive tests show chronic hepatitis with moderate or severe necroinflammation with or without fibrosis. For patients who are HBeAg positive, immune-active chronic hepatitis B (also known as the clearance phase) can last for 10 to 20 years, and may be associated with the loss of HBeAg. For patients who are HBeAg negative, immune-active chronic hepatitis B is associated with immune reactivation and is also referred to as HBeAg-negative chronic hepatitis B or HBeAg-negative replicative phase.

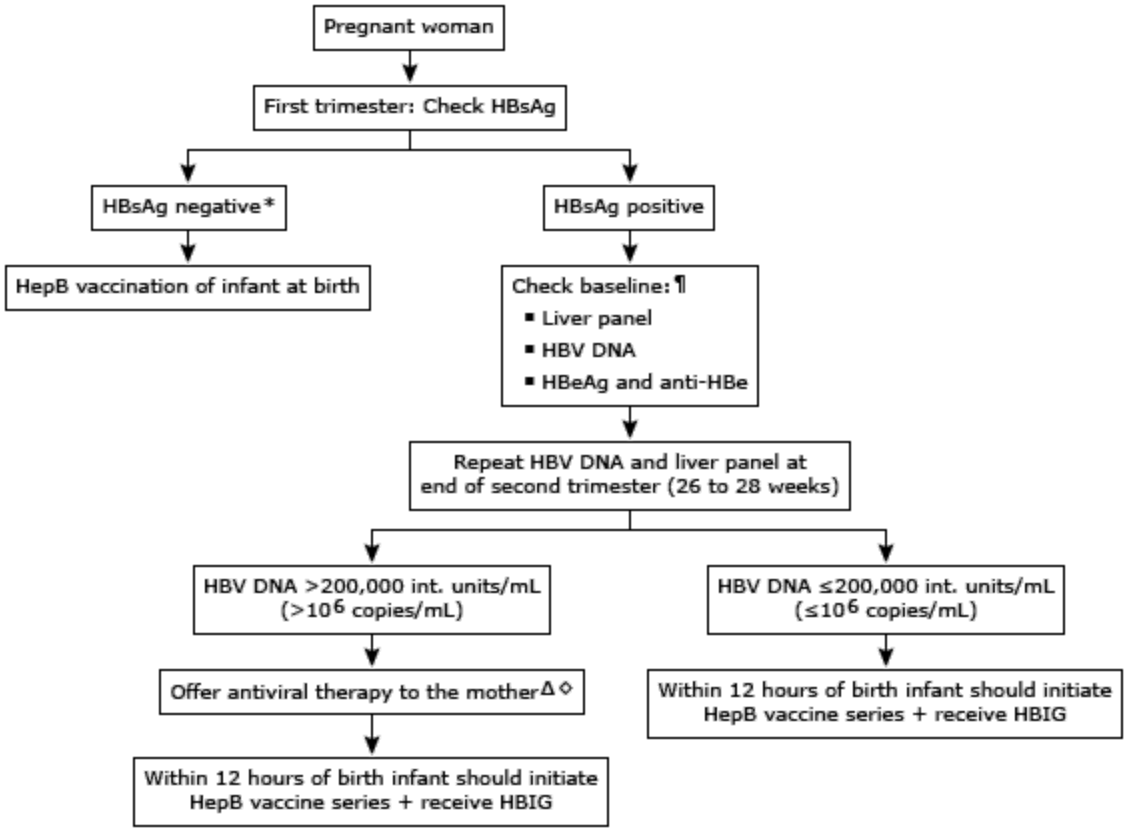
§ Patients with inactive chronic hepatitis B are HBeAg negative. In such patients, liver biopsy confirms the absence of significant necroinflammation, but biopsy or noninvasive testing show variable levels of fibrosis. This stage has also been referred to as the nonreplicative or carrier phase.

References:

1. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*

Graphic 60627 Version 8.0

Algorithm for hepatitis B virus during pregnancy



Anti-HBc: hepatitis B core antibody; anti-HBe: hepatitis B e antibody; anti-HBs: hepatitis B surface antibody; HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

* Check anti-HBs and anti-HBc if mother is at high risk for HBV infection (eg, injection drug user, sexual partner or household contact has chronic HBV). Mothers with no evidence of prior HBV infection (ie, negative for HBsAg, anti-HBs, and anti-HBc) should be vaccinated. In addition, such women should have HBsAg repeated late in pregnancy (approximately 28 weeks).

¶ Women who have a high HBV DNA (>200,000 int. units/mL), elevated aminotransferase levels, and/or a positive HBeAg should be referred to a hepatologist to see if early initiation of antiviral medications is needed.

Δ Start at 28 to 30 weeks gestation. We prefer tenofovir disoproxil fumarate rather than other antiviral agents. Refer to the topic on Hepatitis B and pregnancy for a more detailed discussion of treatment.

◇ For those who continue antiviral therapy after delivery, the pros and cons of breastfeeding must be discussed with the mother. Refer to the topic on Hepatitis B and pregnancy for more detailed discussions of breastfeeding.

Graphic 87231 Version 9.0

Groups at increased risk for hepatitis B virus

Individuals at risk for HBV due to vertical transmission (ie, mother to child transmission)
▪ Individuals born in regions with high (≥8%) or intermediate (≥2%) prevalence rates for HBV, including immigrants and adopted children* ▪ Infants born to pregnant persons who are HBsAg-positive¶ ▪ US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥8%)*
Individuals at risk due to horizontal transmission (ie, percutaneous or mucosal exposure to blood or body fluids contaminated with blood)Δ
▪ Household contacts of HBsAg-positive persons ▪ Needle sharing or sexual contacts of HBsAg-positive persons ▪ Individuals who have ever injected drugs ▪ Individuals with multiple sexual partners and/or history of sexually transmitted infections ▪ Men who have sex with men ▪ Inmates of correctional facilities or other detention settings ▪ Individuals with HIV infection◇ ▪ Individuals with current or past HCV infection§ ▪ Individuals with end-stage kidney disease on maintenance renal dialysis
Other individuals
▪ Individuals with elevated alanine aminotransferase or aspartate aminotransferase levels of unknown origin ▪ Individuals who request HBV testing

In the United States, screening for HBV includes[4]:

- **Risk-based screening** – For all individuals (including children and adolescents), screen those who have any of the risk factors listed in the table if they might have been susceptible during the period of increased risk¥. For those with ongoing risk factors (ie, for horizontal transmission) who remain susceptible, continue to test periodically.Δ
- **Universal screening** – For individuals ≥18 years of age, screen at least once in a lifetime. However, for those without risk factors for HBV, screening is generally not needed if there is documentation of completing a hepatitis B vaccine series and evidence of immunity (anti-HBs ≥10 milli-international units/mL) after vaccination.‡
- **Pregnancy screening** – Screen all pregnant people during each pregnancy, regardless of vaccination status of history of prior testing.

Refer to UpToDate content on screening and diagnosis of HBV, HBV immunization, and HBV and pregnancy for more detailed information on screening and vaccination.

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; US: United States; HIV: human immunodeficiency virus; HCV: hepatitis C virus; anti-HBs: hepatitis B surface antibody; anti-HBc: hepatitis B core antibodies; HBIG: hepatitis B immune globulin.

* If HBsAg-positive persons are found in first-generation immigrants of a family, subsequent generations should be tested.

¶ To reduce the risk of perinatal transmission, infants born to HBsAg-positive mothers should receive HBIG and hepatitis B vaccine as soon as possible and within 12 hours of birth and then complete the hepatitis B series. Post-vaccination serology should be obtained at 9 to 12 months. Refer to the UpToDate topic that discusses HBV immunization in infants.

Δ In unvaccinated individuals with ongoing HBV risk through percutaneous or mucosal exposure, hepatitis B vaccine should be initiated at the time of screening; the need for subsequent doses will depend upon the results. Post-vaccination serology should be performed to ensure immunity. For at-risk persons who do not complete the vaccine series, repeat testing should be performed periodically (eg, every 1 to 2 years).

◇ The presence of HBV coinfection informs the choice of antiretroviral regimen. In addition, patients with HIV who are not immune should be vaccinated regardless of age or risk factors, since HBV infection has an accelerated course in coinfected patients.

§ Patients with chronic HBV are at risk for HBV reactivation with direct-acting antiviral therapy for hepatitis C. Refer to the UpToDate topic that provides an overview of the management of hepatitis C infection.

¥ Susceptible persons include those who have never been infected with HBV (ie, HBsAg-negative, total anti-HBc-negative, and anti-HBs-negative) and either did not complete a HepB vaccine series per the Advisory Committee on Immunization Practices recommendations or who are known to be vaccine nonresponders.

‡ For most patients who remain without risk factors for acquiring HBV, repeat screening is not warranted. However, screening prior to blood, plasma, organ, tissue, or semen donation is routinely performed, regardless of the person's prior history. In addition, screening is warranted prior to initiating immunosuppressive therapy (eg, corticosteroids, biologics, cancer chemotherapy, anti-rejection therapies) since persons with HBV are at risk for HBV reactivation. Refer to the UpToDate topic on HBV reactivation.

References:

1. *Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008; 57:1.*
2. *Abara WE, Qaseem A, Schillie S, et al. Hepatitis B vaccination, screening, and linkage to care: Best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167:794.*
3. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*
4. *Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations – United States, 2023. MMWR Recomm Rep 2023; 72:1.*

Graphic 55052 Version 18.0

Recommended schedule of hepatitis B immunoprophylaxis for term infants and preterm infants with birth weight ≥2 kg

Maternal HBsAg status	Single-antigen vaccine*		Single antigen* plus combination vaccine	
	Dose	Age	Dose	Age
Positive¶	1	Birth (≤12 hours)*	1	Birth (≤12 hours)*
	HBIGΔ	Birth (≤12 hours)	HBIGΔ	Birth (≤12 hours)
	2	1 to 2 months*	2	2 months
	3	6 months◇§	3	4 months
			4	6 months◇§
Unknown¥	1	Birth (≤12 hours)*	1	Birth (≤12 hours)*
	2	1 to 2 months*	2	2 months
	3	6 months◇	3	4 months
			4	6 months◇
Negative	1	Birth (≤24 hours)*	1	Birth (≤24 hours)*
	2	1 to 2 months*	2	2 months
	3	6 to 18 months◇	3	4 months
			4	6 months◇

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HBIG: hepatitis B immune globulin; anti-HBs: antibody to HBsAg.

* Single-antigen vaccines (ie, Recombivax HB or Engerix-B) should be used for the birth dose. Combination vaccines (eg, Pediarix) cannot be administered at birth or before age 6 weeks.

¶ Infants born to HBsAg-positive mothers should receive immunoprophylaxis as recommended whether or not their mother received antiviral therapy during the third trimester.

Δ HBIG (0.5 mL) administered intramuscularly at a separate site (ie, different leg) from vaccine.

◇ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

§ These infants should be tested for anti-HBs and HBsAg at age 9 to 12 months or 1 to 2 months after the last dose of hepatitis B vaccine. Testing should not be performed before age 9 months nor within 4 weeks of the most recent vaccine dose.

¥ Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as

possible but no later than age 7 days.

Adapted from: Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67:1.

Graphic 76345 Version 15.0

Recommended schedule of hepatitis B immunoprophylaxis for preterm infants with birth weight <2 kg

Maternal HBsAg status	Single antigen vaccine*		Single antigen plus combination vaccine*	
	Dose	Age	Dose	Age
Positive¶	1	Birth (≤12 hours)*	1	Birth (≤12 hours)*
	HBIGΔ	Birth (≤12 hours)	HBIGΔ	Birth (≤12 hours)
	2	1 month*	2	2 months
	3	2 to 3 months	3	4 months
	4	6 months◇ §	4	6 months◇ §
Unknown	1	Birth (≤12 hours)*	1	Birth (≤12 hours)*
	HBIGΔ	Birth (≤12 hours)*	HBIGΔ	Birth (≤12 hours)
	2	1 month*	2	2 months
	3	2 to 3 months	3	4 months
	4	6 months◇	4	6 months◇
Negative	1	Hospital discharge or age 1 month*	1	Hospital discharge or age 1 month*
	2	2 months	2	2 months
	3	6 to 18 months◇	3	4 months
			4	6 months◇

HBsAg: hepatitis B surface antigen; HBIG: hepatitis B immune globulin; anti-HBs: antibody to HBsAg.

* Single-antigen vaccines (ie, Recombivax HB or Engerix-B) should be used for the birth dose. Combination vaccines (eg, Pediarix) cannot be administered at birth or before age 6 weeks.

¶ Infants born to HBsAg-positive mothers should receive immunoprophylaxis as recommended whether or not their mother received antiviral therapy during the third trimester.

Δ HBIG (0.5 mL) administered intramuscularly at a separate site (ie, different leg) from vaccine.

◇ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

§ These infants should be tested for anti-HBs and HBsAg at age 9 to 12 months or one to two months after the last dose of hepatitis B vaccine. Testing should not be performed before age 9 months nor within four weeks of the most recent vaccine dose.

Adapted from: Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67:1.

Graphic 55139 Version 12.0

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