Hepatitis B and pregnancy

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All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: May 2017. | **This topic last updated:** Feb 04, 2017.

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 post-partum period, as well as prevention of mother-to-child transmission. 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 "Overview of hepatitis B virus infection in children and adolescents".)
- (See "Acute fatty liver of pregnancy".)
- (See "HELLP syndrome".)
- (See "Intrahepatic cholestasis of pregnancy".)
- (See "Approach to liver disease occurring during pregnancy".)
- (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, HELLP syndrome, and intrahepatic cholestasis of pregnancy. (See "Approach to liver disease occurring during pregnancy" and "Acute fatty liver of pregnancy" and "HELLP syndrome" 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 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 (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 tenofovir disoproxil fumarate 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

Implications of infection

Effect on maternal disease — 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), although flares with serious clinical sequelae appear to be uncommon [6,7]. In a prospective study that followed 126 women during pregnancy and the post-partum period, 2 patients developed a flare during pregnancy whereas 27 (25 percent) developed a flare in the post-partum period [7]. 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 corticosteroids in nonpregnant patients with chronic HBV [8-10]. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy", section on 'HBV flare'.)

  Predictors of HBV flares during pregnancy have not been established. However, flares appear to be more common in women who are hepatitis B e antigen (HBeAg)-positive [7]. 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 [8,11]. (See "Clinical manifestations and natural history of hepatitis B virus infection", section on 'HBeAg-negative chronic hepatitis'.)

- **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 angioma.

- **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 [12,13].

Effect on pregnancy outcomes — For mothers with chronic HBV, the impact of HBV infection on newborns is not well defined and data are conflicting [14-21]. As an example, one large study compared 824 hepatitis B surface antigen (HBsAg) -positive women with 6281 HBsAg-negative controls [18]. 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 [14,15,19], increased risk of prematurity [20], lower birth weight [21], and antepartum hemorrhage [19].

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. 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 [22]. 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 — 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.

Women who are pregnant — Some women 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. Alternatively, 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, 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 [23]. (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 are generally the same as those for patients who are not pregnant; however, some scenarios may differ. As examples:

  - Although antiviral therapy is recommended for most patients with an ALT >2x the upper limit of normal, women without evidence of cirrhosis may choose to defer therapy until after delivery if they have low viral loads and have mild disease activity (eg, aminotransferase levels just above the treatment threshold).

  - Women with high viral loads should initiate therapy in the third trimester, even if the aminotransferase levels are normal, to prevent transmission to their child. (See 'Maternal antiviral therapy' below.)

  Tenofovir disoproxil fumarate is preferred if antiviral therapy is contemplated in pregnant women because of its potency, safety profile, and low risk of resistance. (See 'Safety of antiviral agents in pregnancy' below and "Hepatitis B virus: Overview of management", section on 'Overview of antiviral agents'.)

- **Monitoring women without indications for antiviral therapy** — Women who are not on antiviral therapy during pregnancy should be monitored closely to evaluate for a flare (see 'Effect on maternal disease' above):

  - We obtain liver biochemical tests every three months during pregnancy and for six months postpartum.

  - 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' below.)

- **Women with cirrhosis** — The management of cirrhosis in a pregnant woman does not differ from that of non-pregnant patients. Variceal screening with endoscopy is still recommended and is safe during pregnancy. Active variceal bleeding should be managed the same way with banding or sclerotherapy. Indications for use of beta blockade for prophylactic or post-variceal 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'.)

Women 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, tenofovir disoproxil fumarate is preferred; limited experience supports its safety 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 'Women 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 [24,25]. 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. Carrier 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 post-partum 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 tenofovir disoproxil fumarate, and these are unlikely to have any biologic effects on the nursing infant [26-29]. As an example, one study found that the median breastmilk dose from mothers receiving tenofovir disoproxil fumarate represented 0.03 percent of the proposed oral infant dose, and simulated neonatal plasma concentrations were extremely low [28]. 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 tenofovir disoproxil fumarate [30-33].

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 [28]. Additional discussions of breastfeeding in HIV-infected patients are found elsewhere. (See "Prevention of HIV transmission during breastfeeding in resource-limited settings" and "Antiretroviral and intrapartum management of pregnant HIV-infected women and their infants in resource-rich settings".)

MOTHER-TO-CHILD TRANSMISSION

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 [34]. 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 [35]. 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 IU/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 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 [36].

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 [37]. 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) [38]. A description of the replicative phases of chronic HBV infection is found elsewhere. (See "Clinical manifestations and natural history of hepatitis B virus infection", 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 [39-42]. The risk of HBV transmission is rare when maternal HBV DNA is $<10^5$ to 10^6 int. 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 int. units/mL) to >1400 pg/mL (approximately 45,000,000 int. units/mL) [43].
- 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 int. units/mL ($<10^5$ copies/mL) to 50 percent in those with HBV DNA levels approximately 10^9 int. units/mL (between 9 and 10 $\log_{10}$ copies/mL) [44].
- A study conducted in Australia that included 138 babies born to HBV DNA-positive mothers showed a similar trend [45]. 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 [46]. 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 $2x10^4$, $2x10^5$, $2x10^6$, $2x10^7$, and $2x10^8$ int. 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 [47]. 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 a HBV DNA level $>6x10^7$ int. units/mL. No HBV transmission occurred in mothers with viral loads less than $5x10^7$ int. units/mL, regardless of the mother's HBeAg status.

Transplacental transmission — Transplacental transmission appears to cause only a minority of infections. It can occur due to leakage, such as during a threatened abortion [48,49]. HBV has been found in the villous capillary endothelial cells and the trophoblasts of the placenta [36,50]. 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 [48]. One study found that HBV is able to translocate through the placenta from the mother to the fetal trophoblast [51]. 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 [36,44].

Amniocentesis and other procedures — Transmission following amniocentesis has been described, but the risk appears to be low [52], 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 [53,54] (see "Diagnostic amniocentesis"). 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) [55]. The effect of other invasive procedures during pregnancy (eg, chorionic villus sampling, cordocentesis, fetal surgery) on the risk of transmission is unknown.

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 [56,57]. 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 [58-60]. Thus, cesarean delivery should not be routinely recommended for carrier mothers for the purpose of reducing HBV transmission [24,61].

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 for a relationship between breastfeeding and the subsequent development of chronic HBV infection in the babies [62]. 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 [63]. 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 — Testing for HBsAg should be performed on all women at the first prenatal visit. This blood test will determine whether a woman has current HBV infection and is at risk of transmitting HBV to her infant.

- Women who are HBsAg-positive should have further testing to measure baseline HBeAg, hepatitis B e antibody (anti-HBe), HBV DNA, and aminotransferase levels. Women who have a high HBV DNA (ie, >2x10^5 int. 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' above). In addition, the HBV status of any older children should be evaluated.

  Women 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' below.)

- Women who are HBsAg-negative and are at high risk for HBV infection (eg, injection drug user, sexual partner or household contact has chronic HBV) should be tested for hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc). Mothers without evidence of prior HBV infection or exposure (negative for anti-HBs and anti-HBc) should be vaccinated. In addition, such women should have HBsAg repeated late in pregnancy (approximately 28 weeks). (See "Diagnosis of hepatitis B virus infection", section on 'Who should be tested or screened'.)

Maternal antiviral therapy — We suggest antiviral therapy for HBsAg-positive mothers with high HBV DNA levels, in addition to standard passive-active immunization of the infant, to further reduce the risk of mother-to-child transmission (see 'Newborn immunization' below). This approach is consistent with recommendations by the American Association for the Study of Liver Disease [23]. Patients should be managed in conjunction with a provider experienced in the treatment of HBV. The safety of antiviral agents in pregnancy is reviewed below. (See 'Safety of antiviral agents in pregnancy' below.)

We repeat the HBV DNA level at 26 to 28 weeks for those not already on treatment and initiate therapy thereafter (ie, 28 to 30 weeks) if HBV DNA levels are >2x10^5 int. units/mL (>10^6 copies/mL). We start treatment at the beginning of the third trimester so there is sufficient time for the HBV viral load to decrease, even if the patient delivers early.

For those who require treatment, we prefer tenofovir disoproxil fumarate rather than other antiviral agents since resistance to tenofovir disoproxil fumarate 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 [64-66]. A newer formulation of tenofovir, tenofovir alafenamide, is available. Although there is less bone and kidney toxicity with this agent compared with tenofovir disoproxil fumarate, at this time we do not use tenofovir alafenamide during pregnancy given the lack of sufficient safety data. (See 'Safety of antiviral agents in pregnancy' below and "Tenofovir for the treatment of adults with chronic HBV infection".)

Although other agents (eg, lamivudine, telbivudine) also reduce mother-to-child transmission and appear to be safe when administered during pregnancy [64,67-70], 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. (See "Lamivudine monotherapy for chronic hepatitis B virus infection", section on 'Resistance'.)

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 post-partum [71]. 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 [72].

Regardless of when antiviral therapy is discontinued, women should be monitored for a flare of their HBV disease by measuring the 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'.)

Data from clinical trials and prospective studies that support the use of maternal antiviral therapy to reduce HBV transmission include:

- A meta-analysis of 26 studies, which included 3622 pregnant women, found that 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) [65]. In addition, among mothers who received antiviral therapy and their newborns, there was no increased risk of adverse outcomes (eg, congenital malformations, prematurity, post-partum 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.

- A randomized trial of 200 pregnant women from China who were HBeAg-positive and had HBV DNA >$2x10^5$ int. units/mL (median 10^8 int. units/mL) at baseline received either tenofovir disoproxil fumarate (300 mg) or placebo, starting at 30 to 32 weeks gestation and continuing 4 weeks postpartum [73]. 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 ≥$10^{7.5}$ int. units/mL and were positive for HBsAg and HBeAg [64]. 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 post-partum. 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).

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 1A-B). Infants should then complete the hepatitis B vaccine series. A more detailed discussion of HBV immunization in infants is found elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Routine infant immunization'.)

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 [74]. (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), 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 [71]. (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 [64-70]. Available animal and human data have found no evidence of teratogenicity for tenofovir disoproxil fumarate 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 (www.apregistry.com) 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 [75,76]. As examples:

- Tenofovir disoproxil fumarate – 2.2 percent (67/3007) of infants born to mothers who took tenofovir disoproxil fumarate during the first trimester developed birth defects, and 2.0 percent (28/1412) of infants born to mothers who took tenofovir disoproxil fumarate during the second and third trimester of pregnancy developed birth defects.

- Lamivudine – 3.1 percent (144/4671) of infants born to mothers who took lamivudine during the first trimester developed birth defects, and 2.9 percent (208/7311) of infants born to mothers who took lamivudine during the second and third trimester of pregnancy developed birth defects.

- **Other agents** – For entecavir, only 58 infants were reported to be exposed during the first trimester, and only two during the second or third trimester, with only two birth defects reported in the first trimester group. For adefovir, only 48 infants were reported to be exposed in the first trimester, with no reports of birth defects, and there were no reports of adefovir exposure in the second or third trimester. Four infants were exposed to tenofovir alafenamide (only one in the first trimester), and no birth defects were noted. There were a total of 18 exposures to telbivudine, and no reports of birth defects, but telbivudine had been studied and reported to be safe in several clinical trials [67,68].

- The registry has also collected data on HBV mono-infected patients. Through July 2016, the registry included data for 283 HBV mono-infected pregnancies. Three birth defect cases were reported among 252 live births. There was no pattern among the types of birth defects reported [76].

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 tenofovir disoproxil fumarate 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** – Tenofovir disoproxil fumarate has caused bone abnormalities in the offspring of rhesus monkeys who had been exposed to the drug [77]. The risk of reduced bone mineral density in infants exposed to tenofovir in utero is unclear. Some studies have found no association between tenofovir use during pregnancy and bone loss in infants [78-80]. However, in a study that evaluated 143 newborns born to HIV-infected mothers, the 74 infants who were exposed to tenofovir disoproxil fumarate had a 12 percent lower bone mineral content in the first month of life compared with the 69 who had no tenofovir exposure, even after controlling for potentially confounding maternal and infant factors [81].

- **Effects on growth** – Studies mainly in the HIV population have not revealed an effect of tenofovir disoproxil fumarate on birth weight, although there are conflicting results regarding the effect on head circumference and growth (eg, length) [79,80,82,83]. However, in a study that evaluated 646 HIV-infected pregnant women receiving tenofovir disoproxil fumarate, there was no association between duration of in utero tenofovir exposure and fetal long bone growth, which was assessed using ultrasound [84].

- **Pregnancy loss** – Interferon has been associated with abortifacient effects in rhesus monkeys [74]. There are no such reports in humans [85]; however, since data are limited, all women receiving interferon therapy must use birth control, and interferon must be stopped if women become pregnant. (See 'Women who are pregnant' above.)

SUMMARY AND RECOMMENDATIONS

- 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 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.)

- 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 on pregnancy outcomes' above.)

- 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 'Implications of infection' above.)

- 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, and the risk of developing drug resistance. (See 'Management' above.)

- 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. If antiviral therapy is continued after delivery, low levels of tenofovir are detected in maternal breastmilk, which are unlikely to have any biological effects on the nursing infant. However, data are limited and the decision to breastfeed should be based upon patient preference. (See 'Breastfeeding and transmission' above and 'Breastfeeding' above.)

- 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. (See 'Risk of transmission' above and 'Risk factors for transmission' above.)

- Testing for HBsAg should be performed on all women at the first prenatal visit and repeated late in pregnancy in those at high risk for HBV infection. 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 'Maternal screening' above and "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Routine infant immunization'.)

- 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 int. units/mL (>10^6 copies/mL), we recommend antiviral therapy (**Grade 1B**). We initiate antiviral therapy at 28 to 30 weeks gestation. We prefer tenofovir disoproxil fumarate 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.)

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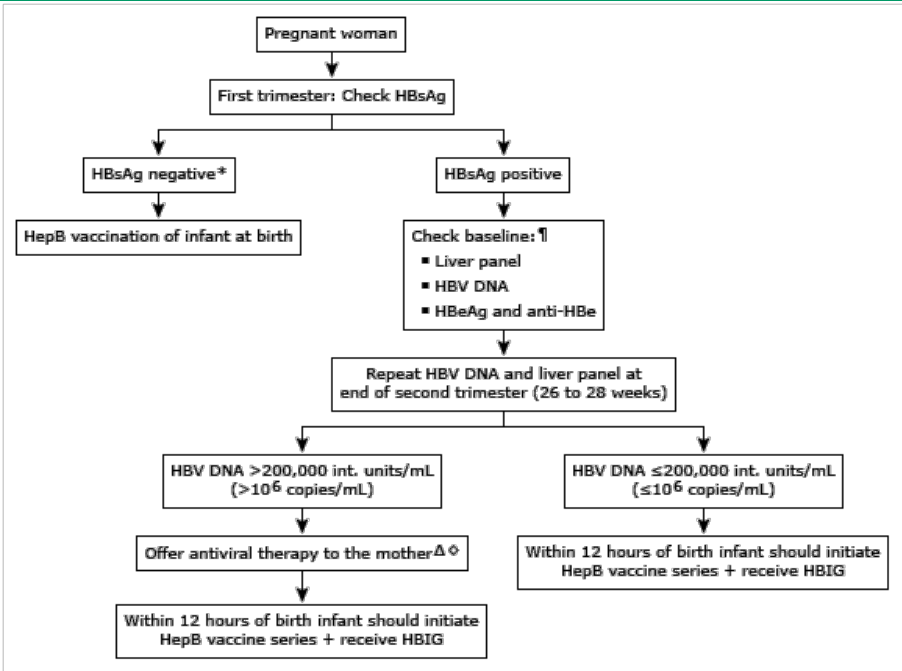
Topic 83476 Version 17.0

GRAPHICS

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.

¶ 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 7.0

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* + combination vaccine	
	Dose	Age	Dose	Age
Positive	1*	Birth (≤12 hours)	1*	Birth (≤12 hours)
	HBIG¶	Birth (≤12 hours)	HBIG¶	Birth (≤12 hours)
	2	1 to 2 months	2	2 months
	3Δ	6 months◇	3	4 months
			4Δ	6 months◇
Unknown§	1*	Birth (≤12 hours)	1*	Birth (≤12 hours)
	2	1 to 2 months	2	2 months
	3Δ	6 months	3	4 months
			4Δ	6 months
Negative	1*	Birth (≤24 hours)	1*	Birth (≤24 hours)
	2	1 to 2 months	2	2 months
	3Δ	6 to 18 months	3	4 months
			4Δ	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.
¶ HBIG (0.5 mL) administered intramuscularly at a separate site (ie, different leg) from vaccine.
Δ 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:

1. *Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: Immunization of infants, children, and adolescents. MMWR Recomm Rep 2005; 54:1.*
2. *Recommended immunization schedule for children and adolescents aged 18 years or younger, United States, 2017. Available at: www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html. Accessed on February 10, 2017.*
3. *Schillie S, Murphy TV, Fenlon N, et al. Update: Shortened interval for postvaccination serologic testing of infants born to hepatitis B-infected mothers. MMWR Morb Mortal Wkly Rep 2015: 64:1118.*

Graphic 76345 Version 11.0

Hepatitis B immunoprophylaxis for preterm infants weighing <2 kg, by maternal HBsAg status

Maternal HBsAg status	Recommendation
Positive	▪ Administer HBIG 0.5 mL + single-antigen hepatitis B vaccine within 12 hours of birth*. ▪ Do not count the birth dose as part of the vaccine series. ▪ Administer three additional hepatitis B vaccine doses with: - Single-antigen vaccine at ages 1, 2 to 3, and 6 months, *or* - Hepatitis B-containing combination vaccine at ages 2, 4, and 6 months¶ ▪ Test for HBsAg and antibody to HBsAg 1 to 2 months after completion of ≥3 doses of a licensed hepatitis B vaccine series (ie, at age 9 to 12 months, generally at the next well-child visit). Testing should not be performed before age 9 months nor within 4 weeks of the most recent vaccine dose.
Unknown	▪ Administer HBIG 0.5 mL + single-antigen hepatitis B vaccine within 12 hours of birth. ▪ Test mother for HBsAg. ▪ Do not count the birth dose as part of the vaccine series. ▪ Administer three additional hepatitis B vaccine doses with: - Single-antigen vaccine at ages 1, 2 to 3, and 6 months, *or* - Hepatitis B-containing combination vaccine at ages 2, 4, and 6 months¶
Negative	▪ Delay first dose of hepatitis B vaccine until age 1 month or hospital discharge. ▪ Complete the hepatitis B vaccine series with: - Single-antigen vaccine at ages 2 months and 6 to 18 months, *or* - Hepatitis B-containing combination vaccine at ages 2, 4, and 6 months¶

HBsAg: hepatitis B surface antigen; HBIG: hepatitis B immune globulin.
* HBIG and hepatitis B vaccine should be administered at different anatomic sites (ie, in different legs).
¶ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

This table is a replacement for Table 4 from: Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States. MMWR 2005; 54:1. A list of the major errata appeared in MMWR on December 7, 2007. The table was updated with information from: Schillie S, Murphy TV, Fenlon N, et al. Update: Shortened interval for postvaccination serologic testing of infants born to hepatitis B-infected mothers. MMWR Morb Mortal Wkly Rep 2015; 64:1118.

Graphic 55139 Version 8.0

Contributor Disclosures

Hannah Lee, MD Nothing to disclose **Anna SF Lok, MD** Grant/Research/Clinical Trial Support: Gilead [HBV/HCV]; Bristol-Myers Squibb [HCV]; Merck [HCV]. Consultant/Advisory Boards: Gilead (declined honorarium) [HBV/HCV]; Tekmira [HBV (Preclinical studies)]. **Rafael Esteban, MD** Grant/Research/Clinical Trial Support: Gilead [Hepatitis B (Viread)]. **Louise Wilkins-Haug, MD, PhD** Nothing to disclose **Jennifer Mitty, MD, MPH** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy