Maternal-to-Child Transmission of Hepatitis B Virus and Hepatitis Delta Virus

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KEYWORDS

• Pregnancy • Hepatitis D virus • Hepatitis B virus • Mother-to-child transmission
• Vertical transmission

KEY POINTS

- The overall rates of chronic hepatitis B in women of childbearing age within the United States has declined, with some increases seen in Appalachian states possibly related to injection drug use. Meanwhile the prevalence of hepatitis delta virus (HDV) in the pregnant population in the United States is largely unknown as HDV testing is underused, including during pregnancy care.
- There are important considerations when caring for pregnant individuals with hepatitis B virus (HBV) which includes the risk of HBV flare, HBV-associated adverse pregnancy outcomes, concern for vertical transmission, and interventions needed to optimize pregnancy outcomes.
- Individuals with hepatitis B and high HBV viral loads are at high risk of maternal-to-child transmission of HBV, but effective interventions exist to decrease risk. Maternal-to-child transmission of hepatitis D is exceptionally rare.

INTRODUCTION

Hepatitis B is a major public health threat, responsible for approximately 820,000 deaths in 2019 alone.[1] It is estimated that approximately 262 million people are living with hepatitis B virus (HBV) infection globally,[2] which includes an estimated 65 million women of childbearing age,[3] with highest prevalence in the Western Pacific Region and African region.[4] In addition, among the reproductive-aged population in certain parts of the United States, there has been an increase in incidence of HBV since

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2009 possibly related to emergent risk factors among young individuals, such as injection drug use (IDU).[5,6]

Hepatitis delta virus (HDV) infection causes the most severe viral hepatitis and rapid progression to cirrhosis and hepatocellular carcinoma (HCC).[7–9] Data on the prevalence of HDV are variable, because HDV screening is largely underused and not widely available in developing regions across the globe,[10] and as a result, there is very scarce data on HDV specifically in women of childbearing age or in the pregnancy setting.

Most cases of chronic hepatitis B (CHB) are contracted under the age of 5 years old, with the majority of cases spread perinatally in endemic regions.[11] In fact, maternal-to-child transmission (MTCT) is responsible for almost half of the chronic HBV infections globally.[12] In the absence of prophylactic treatment, approximately 90% of infants exposed to HBV during delivery develop CHB.[13] Therefore, the World Health Organization (WHO) has placed significant emphasis on the reduction of MTCT to meet their goal of eliminating viral hepatitis as a major public health threat by 2030.[13] Although maternal-to-child co-transmission of HDV is rare, some cases have been reported.[14] Given the severity of the sequela of both HBV and HDV (eg, HCC and cirrhosis), perinatal transmission of HBV and co-transmission of HBV/HDV must be avoided to reduce the global burden of disease of HBV and HDV.

It is important to be aware of HBV and HDV in pregnant patients to effectively reduce the MTCT of these infections. Pregnancy is a critical time to diagnose HBV and HDV and counsel patients on the associated risks. This review evaluates the epidemiology and implications of HBV and HDV in pregnancy, MTCT of HBV and HDV, and the management of HBV and HDV in pregnancy.

EPIDEMIOLOGY OF HEPATITIS B VIRUS AND HEPATITIS DELTA VIRUS IN WOMEN OF CHILDBEARING AGE AND IN PREGNANCY

Hepatitis B Virus

MTCT accounts for approximately half of the CHB cases globally.[12] In 2015, an estimated 65 million women of childbearing age worldwide were chronically infected with HBV.[3] Globally, there are an estimated 4.5 million women with chronic HBV who give birth annually, mostly in African regions and Western Pacific Regions.[15]

Within the United States, there are approximately 1000 cases of MTCT of HBV in the United States each year.[16] The hepatitis B surface antigen (HBsAg) prevalence in pregnant people within the United States between 1990 and 1993 varied from 0.2% to 6%. The highest rates of HBV were found in Asian American (6%) and Black (1%) women while lowest in White (0.6%) and Hispanic (0.14%) women.[17] In a more recent retrospective analysis of HBV in women of childbearing age (15–44 years old) using the national Quest laboratory database from 2011 to 2017, the prevalence of new, chronic HBV (CHB) diagnosis was 0.19% in 2017, which declined significantly from 0.83% in 2011. However, there was an increase in CHB cases in Mississippi, Kentucky, and West Virginia. Rates of acute HBV were stable over time in the country as whole, though Kentucky, Alabama, and Indiana had significant increases ($P < 0.03$).[6] The increase in HBV cases in these particular states is thought to be possibly related to IDU, which also led to previously established increases in HCV rates.

Hepatitis D Virus

Globally, hepatitis D virus affects almost 5% of people with chronic HBV infection.[18] It is estimated that about 12 million people have serological evidence of HDV infection, with the highest concentration in Mongolia, Pakistan, upper Amazonia and Orinoco

River valley, Republic of Moldova, and countries in Western and Middle Africa.[18,19] The true prevalence of HDV in the obstetric population is not entirely clear, as HDV testing is not widely available in resource-limited areas and is not routinely checked in the pregnancy context in developed countries.

However, few studies have shed light on the prevalence of HDV coinfection in pregnant people with HBV in countries in Africa and South Asia (**Table 1**). Within Africa, the prevalence of HDV-antibodies (HDV-Abs) in pregnant women with HBsAg in the public health care setting in Nouakchott, Mauritania, from 2008 to 2009 was found to be 14.7%,[20] whereas another study conducted in five major cities in Gabon (Libreville, Port Gentil, Lambaréné, Oyem, and Franceville) found that HDV-Ab prevalence in HBsAg-positive pregnant women was 15.6%.[21] In another study conducted in Central Africa Republic, 18.8% of HBsAg-positive pregnant women from six different public health maternity wards in Bangui were found to have HDV-Abs.[22] In South Asia, HDV-Abs were found in 20.3% of HBsAg-positive pregnant women in public sector hospitals in Lahore, Pakistan, between 2016 and 2017.[23]

The prevalence of HDV infection in pregnant persons within the United States is unknown, as HDV testing is not routinely conducted in patients with HBV. In a US Midwestern population of 1007 HBsAg-positive nonpregnant people, it was found that only 121 were actually tested for HDV-Abs.[10] In the general US population, there are mixed findings for the prevalence of HDV-Abs among HBV-infected individuals.[24] According to one study conducted with NHANES data from 2011 to 2016, 42% of adult HBsAg carriers had HDV-Abs.[25] Meanwhile, in a retrospective chart review done in Northern California, 8% of patients with CHB were found to have HDV infection.[26] A large study looking at United States and Puerto Rican American Red Cross Blood services in 1985 found that 3.8% of HBsAg-positive individuals were positive for HDV infection, with significantly higher rates in San Jose and California (12.1%) and significantly lower rates in Alabama, Kentucky, Mississippi, and Tennessee.[27] In a nationwide retrospective study of all veterans who were HBsAg-positive from October 1999 to December 2013, 3.4% had HDV-Abs present.[28] High-quality studies need to be conducted to estimate the true prevalence of HDV in the United States and within the obstetric population in the country. Given that routine HBV screening is recommended in pregnancy, this may be an opportune time to delineate prevalence of HDV among those who screen positive for HBV during pregnancy.

Risk Factors for Transmission of Hepatitis B and D Viruses

Both HBV and HDV are transmitted through exchange of bodily fluids (eg, blood, semen) via percutaneous and mucosal routes.[29] The major risk factors for HBV include perinatal transmission, sexual activity, intravenous (IV) drug use, and occupational exposure. Notable risk factors in endemic regions include household contacts, hemodialysis, transmission from a surgeon,[30] and receipt of organs or blood products.[31]

To become infected with HDV, there must be a preexisting HBV infection. Major risk factors for HDV include IV drug use, history of human immunodeficiency virus (HIV) or hepatitis C virus infection, exposure to infected blood or bodily fluids, and intrafamilial and iatrogenic transmission in more highly endemic areas.[32–37] Although sexual transmission and MTCT are major risk factors for HBV, it is relatively rare to transmit HDV sexually and/or perinatally.[38]

HEPATITIS B VIRUS IN PREGNANCY

There are important factors to consider when taking care of pregnant people with HBV, as summarized in **Box 1**. These include the impact of pregnancy on the course

Table 1
Studies evaluating prevalence of hepatitis delta virus-antibodies in pregnant population

Author and Year	Country	Number of HBsAg-Positive Pregnant Individuals Identified	Prevalence Estimate of HDV-Ab in HBsAg-Positive Pregnant Individuals	Notes
Mansour et al,[20] 2012	Mauritania	109	14.7%	• Prospective study on 1966 subjects and 1020 pregnant people ages 14–47 in Sabkha public health care setting in Nouakchott • HDV-Ab positivity was significantly correlated with age ≥44 y
Makuwa et al,[21] 2008	Gabon	109	15.6%	• Cross-sectional study on 1186 pregnant people ages 14–40 in five main cities of Gabon • HDV-Ab percentage was found to be the lowest in women ages 14–20
Komas et al,[22] 2018	Central Africa Republic	69	18.8%	• Cross-sectional study with historical comparison of 2172 subjects and 874 pregnant people in six public health structures with maternity wards in Bangui • Age, transfusion, tendency to tattoo, and absence of condom use were found to be significant risk factors for HDV infection
Aftab et al,[23] 2019	Pakistan	63	20.3%	• Cross-sectional study of 1394 pregnant people ages 20–40 y old in public sector hospitals in Lahore district • Prevalence of HDV-Ab highest in pregnant women ages 26–30

Abbreviations: HBsAg, hepatitis B surface antigen; HDV-Ab, hepatitis D virus-antibodies.

Box 1
Counseling considerations in hepatitis B virus in pregnancy

Risk of HBV flare

Association of HBV with pregnancy outcomes

Concern for vertical transmission

Interventions needed to optimize pregnancy outcomes

of HBV as well as the impact of HBV on the pregnancy course. There is evidence that changes to the immune system that occur during pregnancy may cause hepatitis flares both during pregnancy and in the postpartum period. Rates of hepatitis flares, loosely defined as an elevation in liver aminotransferase levels above the upper limit of normal, have been reported to range from 6% to 14% during pregnancy and 4% to 50% after delivery.[39–44] In the absence of HDV coinfection or advanced fibrosis, these HBV flares are generally asymptomatic and self-limiting, with very few progressing to jaundice or hepatic decompensation.[39] There is conflicting evidence of risk factors for HBV flares, whereas some studies identified the presence of hepatitis B evelope antigen (HBeAg), younger maternal age,[39,45] and decreased parity[42] as risk factors for HBV flares, others did not.[40] Postpartum HBV flares have also been documented after the discontinuation of antiviral treatment.[46]

There are mixed findings in literature regarding the impact of HBV on the pregnancy course. CHB may increase risk for adverse pregnancy outcomes such as gestational diabetes,[47] antepartum hemorrhage, postpartum hemorrhage, placental abruption,[48] threatened preterm labor,[49,50] intrahepatic cholestasis of pregnancy,[51,52] and miscarriage.[53] In contrast, some studies failed to find correlations between CHB and placenta previa, placental abruption,[54] preterm labor,[47,55] or gestational diabetes.[56] The literature on the effect of HBV infection on infertility is also mixed, with some studies suggesting HBV infection negatively impacts cumulative live birth rates and implantation rates during in vitro fertilization (IVF),[57] whereas others did not find an association between HBV infection and fertility treatment outcomes.[58–60] Interestingly, a few studies found a negative correlation between HBV infection in pregnancy and preeclampsia, suggesting a possible protective effect of pregnancy on preeclampsia.[47,61]

MATERNAL-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS

MTCT is a leading cause of CHB in endemic areas of the world and thus is of critical focus in the strategy to eliminate hepatitis B, a goal the WHO has set to reach by 2030.[62] Vertical transmission can occur at any stage of pregnancy, though most of the cases occur during the peripartum period due to exposure to infected maternal blood and secretions during delivery.[63]

Rates of HBV vertical transmission vary. Without intervention, rates of MTCT vary from 70% to 90% in HBeAg-positive mothers and from 10% to 40% in HBeAg-positive mothers.[63] When implemented correctly, preventive interventions have proven to be effective in drastically reducing MTCT rates. With interventions—such as prenatal screening, antiviral therapy, and vaccination of newborns—transmission can be reduced from 90% to 21% in HBeAg + women and from 30% to 2.6% in HBeAg− women.[63]

Risk Factors for Transmission

There are a few important risk factors to consider for HBV vertical transmission (summarized in **Table 2**). A high HBV viral load, indicated by the presence of HBeAg in

Table 2
Risk factors for maternal-to-child transmission of hepatitis B

Potential Risk Factors for MTCT	Increases Transmission
Biological	
High viral load (HBeAg+)	Yes
Mode of delivery	Inconclusive
Breastfeeding	No
Invasive fetal testing	Potentially for patients with high viral load
PROM	No (with proper prophylaxis)
Social/environmental	
Lack of maternal knowledge	Yes
Lack of formal hospital policies	Yes
High cost/other barriers to access	Yes
Perceived stigma (particularly in developing countries)	Yes

serum, high HBV DNA level, and high quantitative HBsAg levels, increases the risk of vertical transmission.[62,64] Despite studies demonstrating the presence of HBeAg and HBV DNA in a high percentage of HBV-infected mothers' breast milk, breastfeeding does not seem to be a risk factor for transmission. The mechanism remains unclear; however, lactoferrin in breast milk may serve a protective role by inhibiting the amplification of HBV DNA.[65]

There have also been a number of studies conducted evaluating whether mode of pregnancy delivery affects transmission. Given that the risk of MTCT is largely due to infant exposure to vaginal blood and secretions at the time of delivery, cesarean sections should theoretically reduce risk of vertical transmission. A systematic review from 2008 showed that elective cesarean delivery (ECD) could prevent MTCT, with no instances of postpartum morbidity as a result of the ECD, though the review noted bias and lack of quality in all the included studies.[66] However, other studies showed that cesarean delivery did not affect the risk of transmission or that the reduction was not significant.[67] Given the paucity of research pertaining to this issue, the conflicting results of the studies that have been conducted, and the fact that cesarean delivery comes with its own risks, the Society for Maternal-Fetal Medicine does not advise clinicians to recommend cesarean delivery for the sole purpose of reducing the risk of vertical HBV transmission.[68]

Similarly, researchers have speculated whether premature rupture of membranes (PROM) in delivery increases the risk of HBV vertical transmission. Studies have found no increased risk of transmission when prophylaxis strategies are implemented.[69]

Another potential risk factor to consider is invasive fetal testing, such as amniocentesis or chorionic villus sampling. Although many earlier studies showed no increase in risk, newer studies demonstrate risk for infected mothers with viral load greater than 7 log 10 copies/mL.[70]

From a socioeconomic and environmental perspective, the lack of maternal knowledge regarding HBV infection, management, and transmission poses a significant risk for MTCT, particularly in endemic countries. For example, in Nigeria, 76% of mothers had suboptimal HBV knowledge. In North America, higher percentages of mothers asserted knowledge, though knowledge gaps do exist.[71] Similar challenges have been reported in Uganda—only 8.3% of women were screened for HBV in their current pregnancy and only 15.6% were aware of HBV screenings; age of respondents,

partners' education, perceived risk, and access to screening services were positively associated with HBV screening.[72] A study conducted in Ghana also showed that social stigma impedes testing.[73] A lack of formal hospital policies regarding HBV prophylaxis represents another risk factor. A 2006 survey across 242 delivery hospitals in the United States found significant gaps in hospital policies and practices regarding HBV vaccination and hepatitis B immunoglobulin (HBIG). Among infants who were born to HBsAg-positive women, only 62.1% received hepatitis B vaccine and HBIG within 12 hours.[74] Cost and access are other barriers to effective implementation of interventions—providing pregnant individuals with free HBsAg screening, HBV vaccination if nonimmune, and administration of HBIG for newborns is important.

EFFECTS ON INFECTED INFANTS

The implications of transmission of hepatitis B to infants are profound—according to the Center for Disease Control and Prevention, infants infected with HBV have a 90% chance of progressing to chronic infection, and when left untreated, 25% will die of liver-related complications.[75] Increasing the rates of infection in infants contributes to greater risk of horizontal transmission among children as well.

Reducing MTCT is a major priority in eliminating hepatitis B worldwide by 2030 and thereby reducing the burden of chronic liver disease and HCC. Although comprehensive guidelines to minimize MTCT have been developed, access to care and effective implementation remain a challenge worldwide.

HEPATITIS DELTA VIRUS IN PREGNANCY

Data regarding maternal hepatitis D infection in pregnancy are scarce. Similar to HBV infection, hepatitis D infection in pregnancy is generally well tolerated. However, hepatitis D virus is associated with more severe liver disease, including higher chance of progression to cirrhosis within 5 years and HCC within 10 years. Cirrhosis is known to lead to adverse pregnancy outcomes such as increased risk for preterm delivery and low birth weight.[76] Thus, while not included as part of current recommendations for the management of HBV or HBV/HDV infections during pregnancy, prenatal screening for HDV in HBsAg-positive mothers is crucial.[77]

Vertical transmission of HDV is rare. A study from 1988 showed that with prophylaxis, 0 of 16 infants exhibited serological evidence of HBV and HDV infection at 7 months.[78] A more recent study from 2004 to 2015 revealed similar results.[38] This rarity could be due in part to the fact that HBV load levels have been found to be lower in HBV/HDV coinfected patients. In addition, a cross-sectional study showed that both viruses were only active in about 40% of coinfected patients, and HDV alone was only active in about 30%.[79] **Box 1 Table 3**, for overview of these studies.

The same strategies used to prevent MTCT of HBV are effective in preventing transmission of HDV as well.

Table 3
Studies investigating efficacy of maternal-to-child transmission of hepatitis D

Study	Results	Takeaway
Ramia et al,[78] 1988	No infants exhibited serological evidence of HBV and HDV infection at 7 months follow-up	HDV MTCT is exceptional
Sellier et al,[38] 2017	HDV Ab was negative in 36 children	HDV MTCT is exceptional

MANAGEMENT OF HEPATITIS B VIRUS AND HEPATITIS DELTA VIRUS IN PREGNANCY

HBV infection during pregnancy presents with special considerations and management issues for both the mother and the fetus. The prevention of MTCT is at the forefront, especially as vertical transmission is responsible for approximately half of chronic HBV infections worldwide.[12] Screening prenatally, early linkage to care with a hepatologist, monitoring for hepatitis flares, antiviral treatment for mothers with high HBV DNA levels, and administering passive–active immunization to newborns are all important components of effective disease management in pregnancy. Clinic care points can be found in Table 4.

Table 4
Recommendations for management of hepatitis B and hepatitis D viruses in pregnancy

	Overview of Recommendations
Screening	• All pregnant patients should be screened at initial prenatal visit for HBsAg • In high-risk populations[a], additionally screen for anti-HBs and anti-HBc to determine immune status
Vaccination	All nonimmune pregnant patients should be vaccinated against HBV
Initial testing	In newly HBsAg-positive pregnant patients, obtain and test for: • HBV DNA • Anti-HBs • Anti-HBc • Anti-HBe • Liver panel (ALT, AST, total bilirubin) • HCV • HIV • HDV antibody
Referral to hepatology	Refer pregnant patient to hepatologist if HBV DNA >200 000 IU/L, liver tests are elevated, HBeAg is positive, or coinfected with HCV or HDV
Monitoring	• Obtain a liver panel every 3 months during pregnancy and up to 6 months postpartum ○ If elevated, follow-up with HBV DNA levels • At 26 to 28 wk gestation, measure HBV DNA levels to determine whether to initiate peripartum antiviral therapy
Initiation of antiviral therapy	Initiate antiviral therapy with TDF if HBV DNA > 200 000 IU/mL or HBeAg-positive
Discontinuation of antiviral therapy	Discontinue antiviral therapy at the time of delivery or within 4 wk postpartum
Newborn immunoprophylaxis	Within 12 hours of birth: • Active immunization with birth dose of HBV vaccine • Passive immunization with 100 IU HBIG Following birth: • Completion of HBV vaccine series
Lactation	If a newborn has received immunoprophylaxis, breastfeeding is safe

Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; anti-HBe, hepatitis B evelope antibody; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TDF, tenofovir disoproxil fumarate.

[a] High-risk populations include IV drug users, pregnant individuals with sexual partners, or household contacts with hepatitis B infection, those with multiple sexual partners in the last 6 months, or those recently evaluated for or treated for a sexually transmitted infection.

Screening and Surveillance

All pregnant women presenting for their first prenatal visit should be tested for HBsAg. The presence of HBsAg establishes the diagnosis of HBV infection. Although universal neonatal HBV vaccination has been implemented in many countries including the United States, universal screening for HBV during pregnancy allows for additional preventative measures. Any patient not tested prenatally should be tested at the time of hospital admission for delivery.[80] In addition to screening for HBsAg, in high-risk populations (eg, IV drug users, sexual partners, or household contacts with CHB, multiple sexual partners in the past 6 months, or recently evaluated or treated for a sexually transmitted infection), testing for hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc) is recommended as it helps determine immune status. HBV vaccination should be offered during pregnancy for those not immune.

If a pregnant individual is found to be positive for HBsAg, additional testing should be conducted, including HBV DNA, anti-HBs, anti-HBc, HBeAg, anti-HBe, and baseline liver panel. Patients should be referred to a hepatologist to determine the need for early initiation of antiviral therapy if HBV DNA greater than 200 000 IU/L, liver tests are elevated, or HBeAg is positive. Furthermore, screening for HDV, hepatitis C virus, and HIV infections should also be conducted as coinfection can significantly worsen outcomes.[24] HDV testing should start with screening for anti-HDV-Abs in serum; if positive, verify for active disease with HDV RNA (qualitative or quantitative).[24] Sexual partners of HBsAg-positive patients should also be assessed for HBV infection or immunity and receive the HBV vaccine if appropriate.

If HBsAg-negative without evidence of prior HBV infection (negative for anti-HBs or anti-HBc) or HBsAg-negative but only anti-HBc-positive, the patient should be vaccinated.[77] For those with the evidence of prior HBV infection, HBsAg screening should be repeated again at 26 to 28 weeks gestation. If at that time HBV DNA $\geq$ 200 000 IU/mL, prompt antiviral treatment should be initiated.[77]

Monitoring Hepatitis B Virus Infection During Pregnancy

Although acute HBV infection during pregnancy is generally mild and not associated with an increased risk of mortality or teratogenicity,[81,82] there is still a risk of MTCT, particularly if the infection is acquired later in pregnancy.[83] In those with CHB, pregnancy can precipitate hepatitis flares, particularly in pregnant individuals without indication for antiviral therapy. For both acute and chronically HBV-infected patients, serial monitoring should be performed throughout pregnancy. Liver biochemical tests should be obtained every 3 months during pregnancy and up to 6 months postpartum. HBV DNA should be measured whenever there is an elevation in alanine aminotransferase (ALT). At the end of the second trimester (26–28 weeks), DNA and aminotransferase levels should be tested to determine the need for initiation of antiviral therapy before delivery.

Recommendations for Initiation and Choice of Antiviral Therapy

In addition to passive–active immunization of newborns, antiviral therapy during pregnancy further reduces the risk of perinatal transmission of HBV.[84–87] The duration of therapy and choice of antiviral medication are important considerations when deciding to initiate antiviral therapy.

Pregnant patients who meet standard indications for HBV therapy should be treated (eg, ALT > 2 times the upper limit of normal, HBV DNA > 20000 IU/mL if HBeAg-positive, HBV DNA > 200000 IU/mL if HBeAg-negative, acute liver failure, or cirrhosis).[77] For those without active or advanced CHB and who do not meet

indications, the decision to initiate antiviral therapy should be deferred until the end of the second trimester when HBV DNA is retested.[84] If HBV DNA greater than 200000 IU/mL on retesting at 26 to 28 weeks gestation, antiviral therapy should be offered.[88] This HBV DNA level threshold is based on an increased risk of transmission at these high viral loads, despite passive–active immunization in infants.[89,90] In areas where HBV DNA may not be available, screening for HBeAg is a suitable alternative to assess eligibility for antiviral prophylaxis.[15,91] Other considerations for starting antiviral therapy before delivery include threatened preterm labor, prolonged uterine contractions, and a child who failed immunoprophylaxis previously.[92]

The choice of antiviral therapy should weigh risk of teratogenicity, adverse effects, and safety profile as well as risk of resistance. Lamivudine, telbivudine, and tenofovir disoproxil fumarate (TDF) have all been shown to effectively reduce the MTCT of HBV.[88,93] A major concern for lamivudine is however its lower barrier of resistance.[94] Although human studies support its safety in pregnancy, adverse events have been observed in some animal studies. There is no evidence of teratogenicity for TDF or telbivudine. Renal and bone toxicity are among the concerns for TDF use. Although a study of HIV-infected pregnant mothers given TDF antiviral prophylaxis saw 12% lower whole body bone mineral content in exposed infants as compared with unexposed infants,[95] a subsequent study with 2 year follow-up showed no significant differences in bone growth.[96] This suggests that any impact on bone toxicity may be transient. Two randomized controlled trials of MTCT with TDF prophylaxis demonstrated no significant differences in the rates of prematurity, congenital malformations, or Apgar scores between exposed and unexposed infants.[85,97] A network meta-analysis also showed that tenofovir is more effective than lamivudine and telbivudine in preventing MTCT.[98] Overall, due its efficacy, safety profile, and lower risk of resistance, TDF is the preferred agent for antiviral therapy during pregnancy.[85,88,97,99] Lamivudine may be a good option in special circumstances, such as if cost is a barrier or if treatment will definitely last less than 3 months.

Tenofovir alafenamide fumarate (TAF) is a new, more stable formulation of TDF that delivers active metabolite more efficiently to hepatocytes. This allows for similar antiviral activity at a lower dose, meaning less systemic exposure and thus decreased renal and bone toxicity.[77] Emerging literature on the use of TAF during pregnancy is promising; TAF is equally as effective as TDF in blocking MTCT of HBV while also being superior with regard to renal safety and breastfeeding.[100–104] **Table 5** provides a summary of studies of TAF use during pregnancy in HBV-infected mothers. More safety data for pregnancy are needed, and HBsAg-positive patients on TAF should switch to TDF when they become pregnant.[94]

If not already on TDF during pregnancy, TDF antiviral prophylaxis should begin at 28 to 30 weeks gestation to allow sufficient time for viral load to decline to less than 200 000 IU/mL.[94] If antiviral therapy is initiated during third trimester to decrease the risk of MTCT, The American Association for the Study of Liver Diseases recommends cessation of antiviral therapy occurs at the time of delivery or within 4 weeks, given that studies have not shown a reduction in the frequency of hepatitis flares with longer duration regimens.[44,77] If cessation of therapy occurs, there should be close monitoring for HBV flares thereafter.

For patients who become pregnant while already receiving antiviral therapy, the risks and benefits of continuing treatment need to be weighed. Patients who need to continue treatment during pregnancy and are on another antiviral medication should be switched to TDF and monitored closely during the transition period to ensure viral suppression.

Table 5
Summary of studies evaluating the safety of tenofovir alafenamide fumarate during pregnancy in hepatitis B surface antigen-positive mothers

Study	Design	Summary of Findings
Han et al,[102] 2022	Initiation of TAF at 24–28 wk gestation (n = 89)	• TAF therapy prevented MTCT with no safety concerns for mothers and infants
Chen et al,[103] 2021	*Group 1* (n = 31): TAF initiated during early pregnancy *Group 2* (n = 57): TAF initiated during middle pregnancy	• Initiation of pregnancy in early and middle pregnancy seems to be safe for both mothers and infants • TAF blocks MTCT of HBV and controls maternal infection
Li et al,[100] 2021	Initiation of TAF or TDF at 24–25 wk gestation *Group 1* (n = 36): TDF *Group 2* (n = 36): TAF	• TAF was superior to TDF with regard to renal safety and breastfeeding • Both TAF and TDF block MTCT of HBV • No significant differences in ALT, total bilirubin, serum creatinine, or BUN levels
Zeng et al,[104] 2021	Initiation of TDF or TAF at 24–35 wk gestation *Group 1* (n = 115): TAF *Group 2* (n = 116): TDF	• Use of TAF during pregnancy reduced MTCT of HBV and is safe for both mothers and infants • TDF group had safety profiles comparable to TAF group
Ding et al,[101] 2020	Initiation of TAF at 24–30 wk gestation (n = 71)	• TAF for highly viremic mothers prevents MTCT of HBV • No safety concerns for either mothers or infants at 24–28 wk follow-up

Abbreviations: BUN, blood urea nitrogen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, maternal-to-child transmission; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

There are currently no HDV-specific guidelines or treatment options for pregnant patients coinfected with HBV/HDV. The recent approval of bulevirtide for treatment of HDV infection in Europe and ongoing trials on its safety and efficacy in adults gives hope for possible future HDV-specific interventions in pregnancy. Given that vertical transmission of HDV is rare and more likely to occur if HBV levels are high,[105] antiviral therapy for HBV, as well as infant immunoprophylaxis, should minimize the risk of MTCT of HDV.

Recommendations for Interventions in Infants to Prevent Maternal-to-Child Transmission

All infants of HBsAg-positive mothers should receive both active and passive immunization at two different sites within the first 12 hours of life.[106,107] Current recommendations include 100 IU of HBIG and a birth dose of HBV vaccine (administered regardless of infant birth weight). This combination effectively reduces the rate of vertical transmission from 90% to 10% in infants whose mothers HBV DNA levels less than 200 000 IU/mL. However, there are emerging data that suggest that HBIG may not be necessary for prevention of MTCT if tenofovir antiviral therapy is initiated at least 4 weeks before birth.[108] Conversely, there is contrasting evidence demonstrating

that if active and passive immunization are provided within less than 2 hours of life (rather than 12 hours), antiviral therapy may not be necessary.[109] Regardless, in conjunction with interventions at birth, close follow-up with a pediatrician and completion of the HBV vaccine series are vital. In the United States, all HBsAg-positive pregnant individuals should be referred to their jurisdiction's perinatal hepatitis B prevention program for case management to ensure that their infants receive timely prophylaxis and follow-up.[77] Given the rarity of vertical transmission of HDV and that routine immunization for HBV also protects against HDV, there are no special considerations for infants of HBsAg-positive mothers coinfected with HDV.

Infants who receive active and passive immunization at birth can be breastfed.[87,110,111] Breastfeeding does not seem to increase the risk of HBV transmission.[87] For patients on antiviral therapy while breastfeeding, studies support the safety of breastfeeding. For instance, only levels of TDF have been detected in the breast milk of women receiving TDF, and given the low levels, it is unlikely that there is any biological effect on the infant.[112–115] Even in HBV/HDV coinfected mothers,[116] decision to breastfeed should ultimately be based on the patient preference and discussion of benefits of breastfeeding, availability of alternatives, and need to continue antiviral treatment after delivery.[116] Mothers should prevent bleeding from cracked nipples and should not participate in donating breast milk.

SUMMARY

Despite significant public health efforts to combat HBV, it remains an important contributor to the global burden of disease and has required special attention to certain subpopulations, such as women of childbearing age. Pregnant individuals living with CHB are at increased risk for hepatitis flares and adverse pregnancy outcomes. Reducing maternal-to-child transmission of HBV is also a major priority, particularly given that almost half the cases of CHB worldwide occur due to perinatal transmission. Management of hepatitis B infection in pregnancy is complex, requiring clinicians to balance the well-being of both the mother and the infant. However, with a careful individualized treatment plan that considers the use of antiviral therapy perinatally and ensures passive–active immunization, successful pregnancy with healthy offspring can be achieved. In contrast to the robust data on the prevalence of HBV, its impact on pregnancy outcomes, and guidelines for its management during pregnancy, there remains a paucity of literature on HDV in pregnancy. To better inform guidelines, future studies should investigate pregnancy course in those infected with HDV, its possible association with adverse pregnancy outcomes in comparison to HBV, and safety of HDV-specific antiviral treatment during pregnancy.

DISCLOSURE

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CLINICS CARE POINTS

- All pregnant patients should be screened at initial prenatal visit for HBsAg.
- All non-immune pregnant patients should be vaccinated against HBV.

- In pregnant patients that are newly HBsAg positive, obtain and test for: HBV DNA, anti-HBs, anti-HBc, anti-HBe, HCV, HIV and HDV antibody, and a liver panel.
- Pregnant patients with HBV DNA > 200,000 IU/L, elevated liver tests, positive HBeAg or co-infection with HCV or HDV should be referred to a hepatologist.
- Liver function should be monitored every 3 months during pregnancy and up to 6 months post partum; elevations should prompt follow up with HBV DNA levels.
- Pregnant patients with HBV DNA > 200,000 IU/ml or positive HBeAg should be started on antiviral therapy with TDF, which should be discontinued at time of delivery or within 4 weeks postpartum.
- Within 12 hours of birth, active immunization (HBV vaccine) and passive immunization (HBIG) should be initiated.
- Newborns who received immunoprophylaxis are safe to breastfeed.

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