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Treatment and Prevention of Viral Hepatitis in Pregnancy

Jodie Dionne-Odom[1,3], **Gabriella D. Cozzi**[2], **Ricardo A. Franco**[1], **Basile Njei**[4], **Alan T.N. Tita**[2,3]

[1]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama

[2]Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Alabama at Birmingham, Birmingham, Alabama

[3]Center for Women's Reproductive Health, University of Alabama at Birmingham, Birmingham, Alabama

[4]Yale Center for Clinical Investigation, Yale School of Medicine, New Haven, Connecticut

Abstract

Viral hepatitis in pregnancy can be caused by a list of viruses that cause systemic infection or target hepatocytes in their pathogenesis. Since viral hepatitis during pregnancy may represent acute, chronic or reactivation of a prior infection, a high clinical suspicion, medical history review, and awareness of risk factors for acquisition of infection are important management principles. The route of infection varies widely from fecal-oral transmission for hepatitis A/E virus to vertical transmission for hepatitis B to bloodborne transmission for hepatitis C to sexual transmission for herpes simplex virus. For this reason, exposure details about travel, food preferences, drug use, and sexual contacts are important to elicit. Although routine prenatal screening is recommended for chronic viral hepatitis caused by hepatitis B and C, most other causes of viral hepatitis in pregnancy are detected in the setting of compatible signs and symptoms (fatigue, abdominal discomfort, jaundice, scleral icterus) or incidentally noted transaminitis on routine labs. Serologic testing is helpful for diagnosis with molecular testing as indicated to guide the management of hepatitis B and C. Preventive vaccines for hepatitis A and B with safety established in pregnancy are recommended in women who are at risk of acquisition. Post exposure prophylaxis for hepatitis A is a single dose of immunoglobulin (IG) and vaccination can be used if IG is not available. Antiviral therapy with tenofovir disoproxil fumarate is recommended as prophylaxis in pregnant women with active hepatitis B and an elevated viral load (>200,000 IU/mL) during the 3rd trimester to prevent vertical transmission. The neonate exposed to hepatitis B at birth should receive IG and monovalent birth dose vaccine within 12 hours, followed by completion of the 3-dose vaccine series. The prevalence of hepatitis C in women of reproductive age has increased in the US and the role of antiviral therapy during pregnancy is of great interest. Cesarean delivery is not currently recommended for the sole purpose of reducing vertical transmission risk in pregnant

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woman with viral hepatitis. Breastfeeding is recommended in women with hepatitis A, B, and C. New and promising prevention and treatment options for hepatitis B/C are under investigation. Investigators and regulatory authorities should ensure that these clinical trials for promising antivirals and vaccines are designed to include pregnant and lactating women.

Keywords

hepatitis A; hepatitis B; hepatitis C; perinatal hepatitis; viral hepatitis in pregnancy

Introduction

Several viruses including hepatitis A, B, C, D, and E viruses as well as viruses in the herpes virus family cause liver disease and these infections can coincide with pregnancy. Acute or chronic liver failure including cirrhosis are associated with the highest risk of adverse pregnancy outcomes. In addition, some of these viruses including hepatitis B and C pose a risk of fetal or perinatal transmission and chronic infection in the offspring and the risk of premature death from cirrhosis and hepatocellular cancer. Herein, we review the contemporary epidemiology, risks of transmission, diagnosis, prevention, management and complications of these viruses in pregnancy.

Hepatitis A

Epidemiology and Transmission

Hepatitis A virus (HAV) is an RNA hepatovirus that is transmitted via the fecal-oral route, usually from ingestion of contaminated food from an infected food-handler or from direct person to person contact. HAV is endemic worldwide and hyperendemic in regions with poor sanitation. In 2018, 12,500 cases of hepatitis A were reported to CDC.[1] The virus has hepatic replication and high levels of virus are shed in the bile and stool of persons with HAV infection. Viral shedding can begin prior to the onset of symptoms. There has been an active outbreak of hepatitis A in the United States since 2016 (genotype 1B) among persons with IV drug use and homelessness.[2] Other women at risk of HAV acquisition in pregnancy include international travelers and those with close contact with international adoptees, military personnel, those with chronic liver disease or HIV infection and employees who work with institutionalized adults. Healthcare workers, daycare workers, and food establishment employees in the US are considered to have low risk of exposure.[1]

Clinical illness with HAV varies widely from asymptomatic infection to icteric hepatitis with liver necrosis and failure which can be fatal in <1% of cases. Most adults have mildly symptomatic infection with fever, malaise, anorexia, and jaundice while most hospitalizations and deaths occur in older adults (age >45). Limited data suggests that pregnant women with acute HAV may be at increased risk of preterm delivery, and that infection in pregnancy is uncommon.[3] Since the period of viremia during early HAV infection is brief, vertical transmission is rare with a single possible US case reported in 1993.[4–6]

Diagnosis and Prevention

HAV has a 4-week incubation period and the diagnosis is generally made by serologic testing with the detection of HAV IgG/IgM. IgM is detectable within one week and antibody levels then decline over the subsequent 4–8 weeks. IgG is detectable within 1–2 weeks of the onset of symptoms and can persist for years after infection, providing lifelong protection against reinfection.[7] Abnormal liver function tests (AST/ALT and bilirubin) are usually elevated prior to symptom onset and resolve within 2–3 months. Molecular diagnostic testing for HAV RNA in blood and stool can also be helpful in establishing the diagnosis but typical use has been limited to outbreak investigations. Some people (10–15%) develop relapsing HAV infection that can persist for up to 6 months.

Management – antepartum, intrapartum and postpartum

Recommended HAV post-exposure prophylaxis (PEP) in pregnancy consists of immunoglobulin administered as a single dose, weight-based IM injection (0.1ml/kg).[1] HAV PEP provides passive and temporary immunity and is 80–90% effective when administered within 14 days of exposure although data specific to pregnant women are limited.

Highly effective, safe vaccines for active immunization have been available for HAV prevention for over 25 years. Current inactivated vaccines are available as monovalent HAV single antigen vaccine (HAVRIX or VAQTA, administered as 2 doses) or dual antigen in combination with HBV vaccine (TWINRIX, administered as 3 doses at 0, 1, 6 months). HAV vaccination recommendations during pregnancy are the same as for non-pregnant women: it is indicated for women who are at risk of infection or severe outcomes who lack evidence of immunity. Risk is defined by travel to regions with intermediate or high HAV endemnicity, drug use, occupational risk, homelessness, HIV and chronic liver disease.[1] Immunity is defined as IgG levels >10 mIU/mL although the precise lower threshold associated with protection is not well established. Vaccination can also be used as post-exposure prophylaxis if immunoglobulin is not available which may be important for women with prolonged periods of exposure to HAV. Common reactions reported after HAV vaccination include fever (16%), injection site erythema (15%) and injection site swelling (10%).[1] A recent retrospective study of the safety of HAV vaccination in pregnant women from the US Vaccine Safety Datalink with 1140 live births included 70% of vaccine exposures occurred during the first trimester. Vaccination in pregnancy was uncommon at a rate of 1.7 per 1000 persons. Although most birth outcomes were not associated with vaccination, an association with small for gestational age (SGA) infants was noted (aOR 1.3, 95% CI 1.1–1.6).[8]

HAV exposed infants can acquire immunity via transplacental antibody transfer. This passive immunity provides protection for several months with undetectable antibody levels by 12 months of age.[1] HAV IgM/IgG and HAV RNA have been detected in breastmilk and breastfeeding is recommended.[9] Details concerning the transmission and recommendations for the diagnosis and prevention of hepatitis A-E during pregnancy are summarized in Table 1.

Hepatitis B

Epidemiology and Vertical Transmission

The global prevalence of HBV infection is approximately 3.5%; Africa (6.1%) and Western Pacific regions (6.2%) are particularly affected.[10, 11] Vertical transmission is a common route of HBV transmission in high (HBsAg prevalence >8%) and intermediate (HBsAg prevalence 2–8%) endemic areas, accounting for almost 90% of the global prevalence. There were 257 million chronic HBV carriers worldwide in 2015, including 65 million women of reproductive age.[10] The average incubation period for HBV infection is prolonged at 120 days. Acute HBV infection early in pregnancy has been associated with a 10% perinatal transmission rate but not with teratogenicity or spontaneous abortion.[12] Vertical transmission of HBV occurs most commonly during perinatal exposure to infected maternal blood and body fluids at the time of delivery.[13] Women with HBV DNA levels >200,000 IU/mL (10^6 copies/mL) have higher risk of vertical transmission and the risk of transmission is neglible (0.04%) below this threshold in exposed infants who received PEP.[14]Infectiousness is also predicted by positive maternal HBV e antigen (HBeAg) serostatus which correlates with elevated HBV DNA levels (>2,000 IU/mL).[13, 15, 16] The risk of developing chronic HBV infection is inversely proportional to the age at time of exposure. Without vaccination, 90% of HBV-exposed neonates will develop chronic infection, compared to 5–10% of HBV-exposed adults.[17, 18]

Pregnancy is generally well tolerated in women with chronic HBV infection who do not have advanced liver disease.[19, 20] Emerging data from cohort studies suggests that women with chronic HBV infection are more likely to have preterm delivery compared to women without HBV.[21] Women with advanced liver disease may experience hepatic flares and decompensation.[20, 22] Long term outcomes of chronic HBV infection include cirrhosis, and hepatocellular carcinoma (HCC). The risk of HCC after perinatal HBV infection is 100 times higher than the risk of HCC following horizontal transmission later in life. With infant immunization programs, the estimated prevalence of HBV infection in children under age 5 has decreased to ~1.3%, compared with ~4.7% in the pre-vaccination era.[23]

Diagnosis and Prevention

Serologic testing for HBsAg in pregnant women is the most common screening strategy for HBV during pregnancy.[24, 25] Germline infection from infected sperm and ovum of HBV carriers is a potential mechanism of in-utero infection. HBV DNA has been identified by in situ hybridization, with a gradient of infected placental cells from the maternal to fetal side which supports intrauterine HBV infection as a mode of vertical transmission.[25–27]

Up to 40% of infants have detectable HBV DNA levels in serum at birth, although not all infants become chronically infected. In-utero transmission can occur in women with very elevated viral load during pregnancy.[28] Invasive prenatal procedures such as amniocentesis, especially in highly HBV viremic women are associated with increased risk of vertical transmission.[29, 30] Counselling before invasive procedures, particularly in the setting of high HBV viral load, and consideration of non-invasive prenatal testing alternatives, is recommended. Universal HBsAg testing during pregnancy enables identification of all

infected women at risk of transmission, providing an opportunity to offer additional preventative measures.[31] HBsAg-positive women should undergo virological (HBeAg and HBV DNA) and biochemical evaluation (ALT level), preferably in the first or second trimester, to identify maternal or fetal indications for antiviral therapy.[31, 32] In a recent meta-analysis with 66 studies, HBeAg screening was an effective marker for vertical transmission risk with a pooled sensitivity of 88% and specificity of 93% in detecting viral load >200,000 IU/mL. Cesarean delivery has not been demonstrated to be beneficial in well-designed trials and is not recommended for the purpose of reducing HBV transmission.[13, 33] There is low risk of transmission of HBV through breastfeeding and the risk of HBV infection is negligible in lactating infants who received immune globulin and vaccine at birth. .[32, 34–36]

Infants are susceptible to HBV infection until they are immunized, especially those born to mothers' positive for HBsAg who lack maternally transferred anti-HBV.[35–37] Hepatitis B immune globulin (HBIG) contains high levels of purified HBsAg-specific antibodies from plasma donors.[12, 13, 32, 38] HBIG provides short-term protection to HBV-exposed neonates for 3 to 6 months after delivery, when provided along with birth-dose vaccination. Universal infant immunization regardless of HBV maternal status, starting with the birth dose, followed by two doses at 1–2, and 6–18 months of age to complete the 3-dose series is the foundation of hepatitis B elimination. In a systematic review of the risk of vertical transmission of HBV in pregnant women with hepatitis B, the estimated transmission rates in the absence of vaccination, with vaccination alone and with vaccination plus the HBIG birth dose were 75%, 21% and 6% in women positive for HBeAg, respectively, and 10%, 3% and 1% in women negative for HBeAg, respectively.[23] The US Centers for Disease Control and Prevention (CDC) recommends that the HBV vaccine birth dose should be given within 12 hours to neonates born to women with HBSAg positivity or women with unknown HBSAg status. Universal HBV vaccination within 24 hours is also recommended for infants weighing >2000 grams who are born to women who do not have hepatitis B.[39] HBV birth dose coverage in the US in 2014 was 72% and initiatives to improve uptake are ongoing.[40, 41]

Antepartum, intrapartum and postpartum management

HBV infection presents with several management challenges affecting both the fetus and mother during pregnancy. These include the effects of HBV viral load and HBV therapies on fetal and maternal health. High maternal serum viral load (HBV DNA level > 200,000 IU/mL) is a common reason for prophylaxis failure, with up to 9% of perinatal transmissions despite both active and passive immunization.[11, 12, 42, 43] Several professional organizations recommend antiviral prophylaxis if the maternal HBV DNA is >200,000IU/ml, as a conservative choice to minimize vertical HBV transmission.[11, 12, 20, 32] Initiation of antiviral prophylaxis at 28–32 weeks' gestational age provides time for suppression of HBV viral load prior to delivery and prevention of vertical transmission. The ideal timing of antiviral initiation and cessation in pregnancy are not yet well defined. Antiviral therapies with efficacy and safety include nucleotide/nucleoside analogue polymerase inhibitors: tenofovir disoproxil fumarate (TDF), lamivudine, and telbivudine.[44, 45] Based on the results of many studies in non-pregnant adults and two randomized controlled trials showing the efficacy and safety of TDF prophylaxis in women with HBeAg+ infection in Asia, TDF is the antiviral

agent of choice for pregnant women.[46, 47] Antiviral resistance to TDF is much less common compared to older antiviral medications. A minor concern with maternal TDF use is the risk of phosphate wastage and secondary osteopenia. Tenofovir alafenamide (TAF), a newer formulation with less renal and bone toxicity was tested in a cohort of pregnant women in China with efficacy and safety demonstrated for perinatal HBV transmission.[11, 45, 48–50] More data on TAF safety and efficacy in pregnancy is needed. A comparison of antiviral prophylaxis guidelines in pregnancy is shown in Table 2.

One important risk of antiviral therapy during pregnancy is the risk of disease flare after the medication is stopped. Hepatic flare is caused by an increase in HBV DNA viral load and host immunologic activity and is defined by an abrupt increase in ALT levels to >5 times the upper limit of normal. Estimates of the prevalence of flare in women range from 4–25%.[51, 52] In terms of management, maternal ALT levels should be followed every 2–3 months for the first six months after cessation of therapy. If the flare persists, restarting the same antiviral therapy used in pregnancy may be helpful.[20, 28]

TDF is secreted in a poorly absorbed form by infants and has minimal transfer into breast milk.[45] Total infant exposure is estimated to be ~0.03% of an oral dose.[53] TAF lactation studies are few.[50] In women without clinical indications for ongoing therapy and whose infants received HBIG and vaccination, TDF can be discontinued at 0–12 weeks after delivery.[53–55] Although HBV is present in breast milk, breastfed infants are at no higher risk of HBV infection than formula-fed infants. Breastfeeding should be initiated without delay. To identify of cases of HBV vertical transmission or vaccination failure, serological testing of infants for HBsAg and antiHBs should be performed at 9–12 months of age, and at least 2 months after completing the primary vaccine course.[54, 56] HBV infected infants require annual monitoring.[54, 56, 57]

Hepatitis C

Epidemiology

Longitudinal data from the National Health and Nutrition Examination Survey (NHANES) has shown that hepatitis C virus (HCV) is most commonly reported blood borne infection in the US.[58] Over time, the estimated disease prevalence has decreased from 3.5 to 2.4 million people, due initially to screening of the blood supply since 1992, and the advent of direct-acting antivirals (DAAs) in 2014.[59] HCV remains a major cause of infectious morbidity and mortality, due to gaps in access to DAAs, increasing rates of hepatic complications, and under-reporting of cases.[60, 61]

In recent years, CDC surveillance systems have detected alarming trends in incident HCV rates: 1) the rate of new HCV infections in 2018 was four times as high as 2010; 2) people of reproductive age born between 1975 and 2000 are responsible for 60% of new diagnosis; 3) injection drug use is the primary route of HCV transmission.[62 63] Among young persons who inject drugs, about 50% are adolescents and women of reproductive age.[64, 65]

HCV vertical transmission rates average 5%; this constitutes the primary HCV transmission route among children.[66] Until recently, routine HCV screening in pregnancy was limited

to women with reported risk factors. Concerns about stigma or legal consequences of risk behaviors led to an under-recognition of cases. HCV prevalence is estimated to be 1–2.5% in the US, and as high as 4% in high risk populations.[67] A recent analysis has estimated that 1700 babies are born with HCV infection in the US each year, based on a 5.8% risk of vertical transmission and 0.7% HCV viremia prevalence among pregnant women.[68] These epidemiological trends prompted the CDC and the US Preventive Services Task Force (USPSTF), in April 2020, to broaden HCV screening recommendations to all pregnant women and adolescents during each pregnancy, except in settings where the prevalence of HCV infection is less than 0.1%.[69]The American College of Obstetricians and Gynecologists (ACOG) also signed on to this recommendation with an updated practice advisory published in May 2021[70, 71]

Pathogenesis

Chronic hepatitis C infection during pregnancy is characterized by a decrease in liver enzymes, while HCV RNA levels may increase 1 to 1.5 log.[72] It is unclear if these alterations are associated with progression of liver disease. HCV infection is independently associated with adverse birth outcomes (low birthweight, small for gestational age, and ICU admission) and gestational diabetes among HCV-infected women with excessive weight gain during pregnancy.[73 74] Women with chronic HCV also have greater odds of developing intrahepatic cholestasis of pregnancy which may increase the risk of fetal distress, preterm birth, or stillbirth.[75 76]

Management

If invasive prenatal diagnostic testing is necessary, amniocentesis is recommended over chorionic villus sampling.[77, 78] Based on limited data, many clinicians avoid internal fetal monitoring and prolonged rupture of membranes in women with chronic active HCV.[79, 80] Cesarean delivery should not be performed solely to reduce maternal-fetal transmission of HCV, given that the exact timing of vertical transmission is unknown.[81, 82] Older cohort studies suggest that there may be a select group of women with elevated HCV viral loads for whom cesarean delivery prior to the onset of labor may be beneficial.[81, 83, 84] Additional prospective, well-designed studies are needed. Breast-feeding is encouraged unless nipples are bleeding or cracked.[85] HCV-infected women should all be counseled to abstain from alcohol. For patients with HCV and normal hepatic function, dose adjustments in most medications are not required, including acetaminophen (maximum dose of 2 g/day). Routine serial laboratory surveillance of liver function or viral load during pregnancy is generally not indicated and women should be referred to a hepatologist or infectious disease specialist. Infants born to women with HCV should be screened for anti-HCV antibodies >18 months of age or for HCV RNA on 2 occasions after 1 month of age.[86]

Treatment

Hepatitis C treatment and achievement of sustained virologic response is associated with reduced risk of liver-related and all-cause mortality.[87, 88] Direct-acting antiviral (DAA) therapy is now recommended for nearly all patients with chronic HCV infection.[89] There are few clinical trials evaluating the safety and efficacy of DAAs in pregnancy. Experience with ledipasvir/sofosbuvir is limited to a recently published phase 1 trial with 100% cure and

no safety concerns.[90] There are no data yet on pangenotypic treatment regimens, and early studies of sofosbuvir/velpatasvir are active (NCT 04382404). In the absence of data, women of reproductive age with HCV should be counseled about the benefit of antiviral treatment prior to pregnancy to improve health and eliminate the risk of vertical transmission. Women who become pregnant while on DAA therapy (with or without ribavirin) should discuss the risks versus benefits of continuing treatment with their physicians. Ribavirin is contraindicated in pregnancy due to teratogenicity risk which persists for up to 6 months after cessation.[89] Research priorities for HBV/HCV are in Table 4.

Other types of Viral Hepatitis

Many other viral infections that cause systemic infection can involve the liver. In this section, we briefly discuss other types of viral infections that can cause hepatitis in pregnancy: hepatitis D and E, viruses in the herpesvirus family (VZV, CMV, EBV) and COVID-19. Information is also summarized in Table 3.

Hepatitis D—Hepatitis D is a viral co-infection that only occurs in people with chronic hepatitis B infection. Global prevalence of infection is low at 0.2% and co-infection occurs in approximately 5% of people living with chronic hepatitis B.[93] Routine antenatal screening is not recommended since vertical transmission of hepatitis D is rare and the management in pregnancy is the same as women with HBV.[94–96]

Hepatitis E—Hepatitis E virus is transmitted via the fecal-oral route and infection can lead to acute hepatitis and fatal liver failure in pregnancy. There are more than 20 million cases of acute hepatitis E annually and transmission is often via contaminated water or uncooked meat (frequently pork) in low and middle-income countries.[97, 98] A recent study documented HEV seroprevalence to be 6.6% among US adults sampled by the NHANES serosurvey in 2009–2012.[99] Most US adults with seropositivity were older (age >60 years) and HEV US cases reported in pregnancy are infrequent. In a recent meta-analysis of reports of HEV infection among >1300 symptomatic pregnant women living in endemic countries, adverse outcomes included fulminant hepatic failure in 45%, maternal death in 26%, fetal death in 33% of cases and evidence of vertical transmission.[91] Unfortunately, ribavirin is the only antiviral with limited efficacy in the treatment of hepatitis E and use of ribavirin in pregnancy is contraindicated. Routine HEV screening in pregnancy is not recommended and vaccination is only licensed and available in China.[92] Little is known about the safety and efficacy of HEV vaccination in pregnancy and a cluster-randomized study among young women in Bangladesh is planned.[93, 94] Since the market for HEV vaccine is considered to be limited, a new vaccine is being tested in China but no companies have trials planned in the US.[95] Diagnosis of HEV can be made by serology, antigen, or PCR testing of serum or stool.

Herpes Virus Family—Viruses in the herpesvirus family (HSV, VZV, CMV, EBV) are common. Pregnant women who lack prior exposure or immunity to herpes viruses are at risk of acute infection that can progress to severe hepatic failure or viral reactivation of a previously acquired infection. Reactivation during pregnancy is most often associated with asymptomatic transaminitis.

Incident herpes simplex virus (HSV1 and 2) hepatitis is rare but serious during pregnancy with associated mortality rates as high as 39%. Pregnancy is a risk factor for acquisition. In a recent review of 56 cases of HSV hepatitis during pregnancy, the average gestational age was 30 weeks and the most common presentation was fever and abdominal tenderness with transaminitis.[101] A high clinical suspicion is useful since early initiation of acyclovir therapy improves outcomes. Serum PCR testing is recommended for diagnosis since serology has limited utility in the setting of acute infection.[102] HSV IgM is a poor test due to a high false positivity rate and it is not recommended by CDC to be used for diagnostic purposes.[103]

Varicella Zoster Virus (VZV) causes chickenpox and universal pediatric VZV immunization has been in place since 1995.[104] Disseminated infection with hepatitis can occur during primary infection and is most common in immunocompromised hosts, but not in pregnant women. Acyclovir is effective treatment for VZV.[105] Acute infection with cytomegalovirus (CMV) and Epstein-Barr virus (EBV) can cause systemic illness with hepatitis but fortunately, infection in immunocompetent hosts is usually benign.[106, 107]

Conclusion

Acute and chronic viral hepatitis in pregnancy is common with most infections caused by HBV and HCV. Transmission routes vary and clinical suspicion is useful since the presentation of infection can range from asymptomatic infection to liver necrosis. Universal screening in pregnancy is recommended by all professional organizations for HBV and by most for HCV. Tenofovir (TDF) prophylaxis reduces the rate of HBV vertical transmission and the role of HCV antiviral therapy is emerging. New options to treat, cure, and prevent viral hepatitis in women before and during pregnancy are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary of Transmission Mechanism and Recommendations for Diagnosis and Prevention of Viral Hepatitis A-E in Pregnancy

Type of Hepatitis	Transmission	Diagnosis	Maternal Prevention	Maternal Treatment	Mode of Delivery	Neonatal post-exposure prophylaxis	Breastfeeding
Hepatitis A[96] (RNA virus)	Fecal-oral transmission due to contaminated food or direct contact with an infected person.	Testing only recommended if symptomatic. Maternal serologic testing for HAV IgM antibodies. Infection is usually brief but can persist for up to 6 months. Those with prior infection or vaccination will have HAV IgG	HAV vaccination in pregnancy is available and recommended for those at high risk of HAV acquisition, pre-existing liver disease or severe outcomes of infection	Supportive Care	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical HAV transmission is NOT RECOMMENDED	HAV IgG 0.1 mL/kg Recommend appropriate hygiene practices by those caring for the neonate	Yes, provided appropriate hygienic precautions taken
Hepatitis B (DNA virus)[96–98]	**1** Parenteral **2** Sexual or environmental with direct contact with infected body fluids (blood, cervicovaginal fluid, semen.) **3** Vertical	Universal screening recommended. Maternal serologic testing for HBsAg. If HbsAg positive, perform additional testing including HBV DNA viral load	HBV vaccination recommended for pregnant women who are HBsAg- and at high risk of HBV acquisition.* Serologic testing for immunity (HBsAb) prior to vaccination is not required but may be cost effective.	Tenofovir Disoproxil Fumarate (TDF) recommended for pregnant women with elevated HBV viral load starting at 28 weeks. Details in table 2.	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical HBV transmission is NOT RECOMMENDED	HBIG and HBV vaccine within 12 hours of birth for infants born to women with HBSAg+ or unknown HBV status. Universal HBV vaccination within 24 hours of birth for medically stable infants >2kg born to women with HBSAg- status. Birth dose vaccine is followed by completion of the 3-dose infant vaccine series.	Yes, provided the infant receives HBIG and HBV vaccination at birth
Hepatitis C[96] (RNA virus)	**1** Parenteral **2** Sexual due to direct contact with infected body fluids (mostly blood). Veryuncommon with vaginal sex in serodiscordant heterosexual couples.	ACOG, CDC, USPSTF recommend universal screening pregnancy. SMFM recommends risk based screening and are reviewing their recommendations. Maternal serologic testing	No maternal vaccination available Risk reduction or avoidance of drug use and/or sex partners with HCV.	Supportive Care Antiviral therapy during pregnancy is under investigation. At this time, use outside of a clinical trial is not recommended	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical HCV transmission is NOT RECOMMENDED	None	Yes, provided there are no cracked maternal nipples

Type of Hepatitis	Transmission		Diagnosis	Maternal Prevention	Maternal Treatment	Mode of Delivery	Neonatal post-exposure prophylaxis	Breastfeeding
	3	Vertical	for HCV Ab by 2nd or 3rd generation enzyme immunoassay (ELISA) If HCV Ab positive, perform HCV RNA PCR testing to assess for active infection. Genotype testing can also be considered.					
Hepatitis D(DNA virus)[99] Incomplete viral particle that only causes disease in presence of HBV	**1** **2** **3**	Parenteral Sexual or environmental with direct contact with infected body fluids (blood, cervicovaginal fluid, semen.) Vertical	Screening is not recommended. Maternal antigen or antibody testing for HDAg in serum or hepatic tissue can be performed. Confirmatory testing with HDV DNA PCR.	Vaccine is not available	Supportive care Treatment protocol for HBV co-infection as above	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical HDV transmission is NOT RECOMMENDED	Neonatal treatment protocol as above for HBV. No treatment specific to HDV.	Yes, provided the infant receives HBIG and HBV vaccination at birth
Hepatitis E(RNA virus)[99,100]	**1** **2** **3** **4**	Fecal-oral Ingestion of raw/ undercooked shellfish or meat Parenteral transmission (infected blood) Vertical/ Perinatal	Maternal serologic testing for HEV IgM antibodies. Confirmatory testing and viral load can be determined with HEV RNA PCR	Vaccine is not available	Supportive care	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical HEV transmission is NOT RECOMMENDED	None	Yes, provided appropriate hygienic precautions taken

HAV: Hepatitis A virus; HAIG: Hepatitis A Immune globulin; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; Anti-HBc: Total Hepatitis B core antibody; IgM Anti-HBc: IgM antibody to the Hepatitis B core antigen; Anti-HBs: Hepatitis B surface antibody; HBIG: Hepatitis B Immune globulin; HCV: Hepatitis C virus; HCV Ab: Hepatitis C antibody; HDV: Hepatitis D virus; HEV: Hepatitis E virus

*Risk of HBV acquisition is defined by: HbsAg+ sexual partner, receiving hemodialysis, HIV positive, >1 sexual partner in the past 6 months, recent sexually transmitted infection, recent injection drug use.

Table 2.

Comparison of US and International Guidelines for Hepatitis B in Antiviral Prophylaxis in Pregnancy to Prevent Transmission

Professional Organization	Strength of Recommendations	Year of Recommendation	Treatment Criteria	Medication of Choice	Duration of Therapy
US Society for Maternal Fetal Medicine (SMFM)[98]	Consider treatment	2016	Viral load >6–8 $\log_{10}$ copies/mL (>5.2 $\log_{10}$ IU/mL)	Tenofovir disoproxil fumarate (TDF) PO daily	≥28 weeks GA - delivery
American Association for the Study of Liver Diseases (AASLD)[101]*	Suggests treatment	2016	Viral load >200,000 IU/mL (5.3 $\log_{10}$ IU/mL)	Tenofovir disoproxil fumarate (TDF) PO daily	Initiation at 28–32 weeks GA. No clear recommendation for when to stop
European Association for the Study of the Liver (EASL)[102]	Recommends treatment	2017	Viral load >200,000 IU/mL or HBsAg levels >4 $\log_{10}$ IU/mL	Tenofovir disoproxil fumarate (TDF) PO daily	24–28 weeks GA and continue for up to 12 weeks after delivery
World Health Organization (WHO)[103]	Recommends treatment	2020	Viral load ≥200,000 IU/mL (≥5.3 $\log_{10}$ IU/mL)	Tenofovir disoproxil fumarate (TDF) PO daily	28 weeks GA – at least until delivery.

Table 3.

Diagnosis, Treatment and Prevention of Other Types of Viral Hepatitis in Pregnancy

Type of Viral Hepatitis	Diagnosis	Maternal Treatment/ Prevention	Mode of Delivery	Breastfeeding
Herpes Simplex (DNA virus)[104]	Serum testing for HSV IgG and DNA PCR in a symptomatic patient with compatible symptoms. Liver biopsy can be considered for histology and PCR testing.	No vaccine is available but is under investigation. Treatment with IV acyclovir	Cesarean delivery is recommended in women with active genital lesions or prodromal symptoms, e.g., vulvar pain or burning Cesarean delivery may be offered for women with primary or non-primary first episode in the third trimester due to the possibility of prolonged viral shedding	Yes, provided no active herpetic lesions on the breast
Cytomegalovirus (DNA virus)[105]	Test if symptomatic or confirmed exposure. Serum quantitative CMV DNA PCR testing. Serial maternal testing for CMV IgM and IgG (with avidity assay) at baseline and in 3–4 weeks	No maternal vaccination available. Supportive care. SMFM does not recommend antenatal treatment with ganciclovir or valacyclovir. Antenatal antiviral ganciclovir therapy should only be offered as part of a research protocol.	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical CMV transmission is NOT RECOMMENDED	Yes, provided appropriate hygienic precautions taken Neonates born at GA <30 weeks or with birthweight <1500g may be at increased risk of late onset sepsis-like syndrome and long term impact on hearing and growth; patients should be counseled on the risks vs benefits of breastfeeding.[106–108]
Varicella Zoster (DNA virus)[105]	Clinical diagnosis in the setting of typical vesicular rash. VZV may also be diagnosed by qualitative viral PCR assay of infected fluids (vesicular fluid, amniotic fluid)	VZV vaccination at age >12 months is recommended to prevent disease in adulthood. VZV vaccination is contraindicated in pregnancy as it is a live, attenuated vaccine. Oral acyclovir initiated within 24 hours of maternal symptom onset is recommended. IV acyclovir may be used in patients with systemic infection. Women who are not immune to VZV and are exposed to someone with primary VZV should receive VZIG within 96 hours. (Up to 10 days permitted).	Per usual obstetric indications. Elective Cesarean delivery for prevention of vertical VZV transmission is NOT RECOMMENDED	Yes, provided no active lesions on the breast

Table 4:

Research Priorities for the Management of Hepatitis B and C in Pregnancy

Hepatitis B	Hepatitis C
Optimize timing of initiation and duration of antiviral therapy to minimize vertical transmission	Development of a safe and effective preventive vaccine
Impact of HBV infection and role of antiviral therapy in improving preterm delivery rates and other birth outcomes	Identify antivirals with safety and efficacy in pregnancy and breastfeeding
Safety and efficacy of tenofovir alafenamide in pregnancy and breastfeeding	Optimize screening guidelines to maximize identification of pregnant women with HCV
Identify subset of women with HBV for whom cesarean delivery may reduce vertical transmission risk	Develop HCV targeted risk reduction for pregnant women who use injection drugs
Reducing/eliminating cold chain requirements for birth dose HBV vaccine	Improve follow up testing rates and identify new prevention options for HCV-exposed infants
Improve uptake of universal birth dose vaccine at delivery	Expand treatment access to women of reproductive age with substance use