HCV in Pregnancy

Testing

Recommendation for Universal Hepatitis C Screening in Pregnancy	
RECOMMENDED	RATING
As part of prenatal care, all pregnant persons should be tested for HCV infection with each pregnancy, ideally at the initial visit (see Recommendations for Initial HCV Testing and Follow-Up).	I, B

It has been estimated that up to 29,000 persons with HCV infection gave birth each year from 2011 to 2014 in the United States (Ly, 2017). Additionally, there has been an increase in HCV among young adults, including persons of childbearing age (Watts, 2017); (Koneru, 2016); (Kuncio, 2016). Identifying HCV infection as people engage in prenatal care would allow for appropriate assessment of liver disease status and ideally facilitate linkage to HCV care after delivery. In addition, prenatal HCV diagnosis is a prerequisite for appropriate screening and care for exposed children. Risk factor-based HCV screening has never been shown to be effective (Kuncio, 2015); (Waruingi, 2015); (Fernandez, 2016) and inconsistent screening and counseling practices have been reported among obstetricians and gynecologists (Boaz, 2003). Consequently, the US Preventative Task Force (Owens, 2020), US Centers for Disease Control (Schillie, 2020), have published recommendations for universal HCV screening of all adults, including screening during prenatal care. In 2021, the American College of Obstetricians and Gynecologists have issued a practice advisory recommending HCV testing for all pregnant persons at the beginning of each pregnancy. This recommendation was reaffirmed in the American College of Obstetricians and Gynecologists 2023 guideline on viral hepatitis in pregnancy (ACOG, 2023). Testing at the initiation of prenatal care is considered optimal to maximize opportunities for education, referral, and appropriate testing for the exposed infant. Early identification is key as persons living with HCV and their exposed infants are at significant risk for not linking to appropriate HCV evaluation or care. Pregnant persons should be tested with an HCV antibody test. If positive, this should be followed with HCV RNA testing.

Pregnant persons with HCV infection should be linked to care so that antiviral treatment can be initiated at the appropriate time (see Testing and Linkage to Care section). Modeling studies demonstrate that universal HCV screening in pregnancy is cost-effective and would reduce long-term morbidity with linkage to care and treatment (Tasillo, 2019). Infants given birth to by a person with HCV infection should be tested and followed as described in the HCV in Children section.

The Society for Maternal-Fetal Medicine recommends several obstetrical practices in pregnant persons with HCV infection, including avoidance of internal fetal monitoring during labor and early artificial rupture of membranes unless necessary in the course of labor management (Dotters-Katz, 2021).

Whom to Treat

Recommendation Regarding HCV Treatment and Pregnancy	
RECOMMENDED	RATING
For persons with childbearing capacity and known HCV infection, antiviral therapy is recommended **before** considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B

Persons with childbearing capacity with HCV infection should be counseled about the benefit of antiviral treatment prior to pregnancy to improve the health of the mother and eliminate the low risk of mother-to-child transmission (MTCT). People 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 its known teratogenicity. In addition, the risk for teratogenicity persists for up to 6 months after ribavirin cessation and applies to people with childbearing capacity taking ribavirin and female partners of men taking ribavirin. If exposed to ribavirin, they should also have their maternal and fetal outcomes reported to the ribavirin pregnancy registry. Also see Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin.

There are no large-scale clinical trials evaluating the safety of direct-acting antivirals (DAAs) in pregnancy. A small study of 9 participants evaluating the pharmacokinetics of ledipasvir/sofosbuvir in pregnancy demonstrated a 100% SVR12 rate and no safety concerns (Chappell, 2020).

A few international case series studies have been reported. A prospective observational study from India enrolled 26 pregnant persons with HCV infection who were treated with 12 weeks of ledipasvir/sofosbuvir after the first trimester. The reported SVR12 rate was 100% (26/26). There were no serious adverse events and no early safety concerns among the participants or their infants. All infants remained HCV RNA negative at the 6-month follow-up (Yattoo, 2023). Another prospective observational case series from Egypt identified 100 persons who experienced an unintended pregnancy while on DAA treatment (95% treated with sofosbuvir/daclatasvir). Ninety-one of these individuals stopped DAA therapy upon discovery of the pregnancy. Nine people made the decision to continue both the pregnancy and DAA therapy; 2 individuals were lost to follow-up after completing HCV treatment. All 7 of the remaining individuals who completed DAA therapy and attended their 12-week post treatment follow-up attained SVR12. All 7 went on to deliver full-term, apparently normal neonates (AbdAllah, 2021). Another case series also from Egypt reported on the safety and efficacy of DAA treatment among 13 pregnant persons (2 of whom had indirect exposure as it was their male partner who was on DAA therapy). Among the 6 pregnant persons who completed 12 weeks of sofosbuvir/daclatasvir treatment in the context of an unintended pregnancy, 5 had subsequent full-term deliveries. One of these neonates had spina bifida. One of the 6 people who completed DAA therapy had a preterm birth; the neonate had respiratory distress (assisted ventilation required) and neonatal jaundice. Among the 5 persons who had 4 weeks to 8 weeks of DAA therapy (treatment discontinued upon discovery of the pregnancy), there were 3 full-term births, 1 stillbirth, and 1 abortion. Of the 2 pregnant persons with indirect DAA exposure, there was a single full-term birth and a single preterm birth without any reported apparent abnormalities. SVR rates were not reported (El-Kassas, 2023). A prospective case series from the US reported on 7 pregnant persons with HCV viremia who opted to pursue DAA therapy antepartum. Planned treatment was 12 weeks of either sofosbuvir/ledipasvir or sofosbuvir/velpatasvir. Only 2 of the 7 attended the 12-week posttreatment follow-up; both attained SVR12. A single preterm birth was reported due to premature rupture of membranes at 32 weeks gestation (Kushner, 2022).

There are currently 2 clinical trials enrolling or in pre-enrollment phases to study the use of pangenotypic regimens during pregnancy. The STORC trial is evaluating the use of sofosbuvir/velpatasvir (NCT#05140941) and is open to enrollment, with interim results of the initial 26 participants treated with sofosbuvir/velpatasvir presented at The Liver Meeting 2024 (Chappell, 2024). The IMPAACT network is planning to launch a phase I/II study of glecaprevir/pibrentasvir treatment during pregnancy (NCT#07040319).

DAA treatment can be considered during pregnancy on an individual basis after a discussion between the pregnant person and their physician about the potential risks and benefits. Data indicate that both pregnant persons and clinicians are receptive to these conversations. Both pregnant persons and clinicians expressed regarding safety, access, and cost (Yee, 2022).

TiP-HepC is an HCV in pregnancy registry that was established to collect and share all available clinical outcomes data on HCV treatment during pregnancy within and outside of clinical trials. Data can be found here.

Monitoring During Pregnancy

Recommendations for Monitoring Pregnant Persons With HCV Infection	
RECOMMENDED	RATING
For pregnant persons who test positive for HCV antibodies, HCV RNA and routine liver function tests are recommended at initiation of prenatal care to assess the risk of mother-to-child transmission and severity of liver disease.	I, B
All pregnant persons with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce mother-to-child transmission.	I, B
In pregnant persons with HCV infection and pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy with subsequent assessment of alanine aminotransferase, aspartate aminotransferase, and serum bile acids.	I, B
Persons HCV infection and cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine obstetrician (ie, a high-risk pregnancy specialist).	I, B

Pregnancy Impact on HCV Infection

Pregnancy itself does not appear to negatively affect chronic HCV infection. In general, serum alanine aminotransferase (ALT) levels decrease during the first and third trimesters of pregnancy and increase after delivery. HCV RNA levels rise during the first and third trimesters, reaching a peak during the third trimester, and decrease postpartum (Conte, 2000); (Gervais, 2000). These effects are likely due to the immunosuppressive effects of pregnancy and increased maternal plasma volume. Compared with pregnant

persons without HCV infection, pregnant persons with HCV infection have a higher incidence of intrahepatic cholestasis of pregnancy (pooled odds ratio 20.40; 95% CI 9.39–44.33) based on a meta-analysis of 3 studies (Wijarnpreecha, 2017). Intrahepatic cholestasis of pregnancy is associated with an increased rate of adverse maternal and fetal outcomes; all individuals with this syndrome should be immediately referred to a high-risk obstetrical specialist for monitoring and treatment.

HCV Infection Impact on Pregnancy and Perinatal Outcomes

In a 2023 systematic review and meta-analysis of 14 studies published between 2000 and 2022, investigators evaluated maternal and perinatal outcomes among pregnant persons with HCV infection compared with pregnant persons without HCV infection. The analysis indicated that maternal HCV infection was associated with an increased risk of preterm birth (pooled odds ratio [OR]1.66; 95% CI 1.59–1.74), intrauterine growth restriction (pooled OR 2.09; 95% CI 2.04–2.14), and low birth weight (pooled OR 1.96; 95% CI 1.63–2.36). A subgroup analysis to assess the possible influence of potential confounders (age, parity, drug and alcohol use, preeclampsia, and HIV and/or hepatitis B coinfection) demonstrated that maternal HCV infection was independently associated with intrauterine growth restriction and low birth weight (Shen, 2023).

Pregnant persons with cirrhosis are at increased risk for poor maternal outcomes (ie, preeclampsia, cesarean section, hemorrhagic complication, and death) and neonatal outcomes (ie, preterm delivery, low birth weight, and neonatal death) (Puljic, 2016); (Tan, 2008). Women with cirrhosis should be counseled about these increased risks and care should be coordinated with specialists in maternal-fetal medicine.

Hepatitis C mother-to-child transmission (MTCT) occurs at an overall rate of 5% to 15% (Jhaveri, 2015); (Shebl, 2009); (Mast, 2005); (Ceci, 2001) with the number that progress to chronic infection being 3% to 5%. No specific risk factor predicts transmission and no specific intervention (eg, antiviral, mode of delivery, or others) has been demonstrated to reduce HCV transmission—except for suppression of HIV replication in women with HIV/HCV coinfection (Checa Cabot, 2013). Given the potential associated risk of MTCT, it is advisable to avoid invasive procedures (eg, fetal scalp monitors and forceps delivery).

The neuropsychiatric and systemic side effects of interferon-based agents and the pregnancy category X rating of ribavirin made studies involving these drugs to interrupt MTCT untenable for safety reasons. It is important to note that DAAs have not been formally studied as a way to interrupt MTCT. DAAs have not demonstrated significant toxicity in animal studies, and antiviral medication use has become the standard of care for people with HIV and hepatitis B infection. Therefore, it is realistic to think that DAAs could be used in the future to interrupt MTCT. However, with a low transmission rate, improved methods to identify mothers who are likely to transmit HCV infection are needed to reduce the number needed to treat below 20 to prevent 1 transmission event. DAA therapy is not currently recommended during pregnancy to reduce MTCT due to the current lack of safety and efficacy data.

Postpartum Issues

Recommendations Regarding Breastfeeding and Postpartum Care for Persons With HCV Infection

RECOMMENDED	RATING
Breastfeeding is not contraindicated in persons with HCV infection, except when there are cracked, damaged, or bleeding nipples, or in the context of HIV	I, B

Recommendations Regarding Breastfeeding and Postpartum Care for Persons With HCV Infection	
coinfection.	
Persons with HCV infection should have their HCV RNA reevaluated after delivery to assess for spontaneous clearance.	I, B

HCV and Breastfeeding

Breastfeeding is not a risk factor for HCV MTCT (CDC, 1998) with studies showing similar rates of maternal infection in breast-fed and bottle-fed infants (Resti, 1998). However, given the associated risks of HCV transmission with blood exposure and HIV transmission with breastfeeding, it is recommended that persons with HCV infection who breastfeed abstain from doing so while their nipples are cracked, damaged, or bleeding, and in the context of HIV/HCV coinfection.

Spontaneous Clearance in the Postpartum Period

HCV RNA levels can fluctuate during pregnancy and the postpartum period. The most frequently observed pattern is a steady rise in HCV RNA levels during pregnancy followed by a slight or significant drop (>3 to 4 $\log_{10}$) in the postpartum period (Lin, 2000). This is most likely due to the release of tolerance in HCV-specific T lymphocyte responses that develop during pregnancy (Honegger, 2013). Spontaneous clearance of HCV can occur in the postpartum period. Previous studies with small numbers of participants demonstrated that up to 10% of postpartum persons became HCV RNA undetectable (Honegger, 2013); (Hattori, 2003); (Lin, 2000). A study from Egypt demonstrated a 25% rate of spontaneous resolution that was strongly associated with the favorable IL28B allele (Hashem, 2017).

Given these findings, postpartum persons should have their HCV RNA re-evaluated after delivery. In that time, HCV RNA could become undetectable or rebound to prepregnancy levels. The possibility of spontaneous viral clearance should be considered for any person who is being assessed for DAA treatment in the postpartum period.

Related References

AbdAllah M, Alboraie M, Abdel-Razek W, et al. Pregnancy outcome of anti-HCV direct-acting antivirals: real-life data from an Egyptian cohort. *Liver Int*. 2021;41(7):1494-1497. doi: 10.1111/liv.14913.

American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy: ACOG clinical practice guideline No. 6. *Obstet Gynecol*. 2023 Sep 1;142(3):745-759. doi: 10.1097/AOG.0000000000005300. PMID: 37590986.

Boaz K, Fiore AE, Schrag SJ, Gonik B, Schulkin J. **Screening and counseling practices reported by obstetrician-gynecologists for patients with hepatitis C virus infection**. *Infect Dis Obstet Gynecol*. 2003;11(1):39-44.

Centers for Disease Control and Prevention (CDC). Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Recomm Rep*. 1998;47(RR-19):1-39.

Ceci O, Margiotta M, Marello F, et al. **Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study**. *J Pediatr Gastroenterol Nutr*. 2001;33(5):570-575.

Chappell C, Charles J, Smid M, et al. Safety, tolerability, and outcomes of sofosbuvir/velpatasvir in treatment of chronic hepatitis C virus during pregnancy: interim results from the STORC study [0222]. Presented at: The Liver Meeting; November 15-19, 2024; San Diego, California.Chappell CA, Scarsi KK, Kirby BJ, et al. **Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study**. *Lancet Microbe*. 2020;1(5):e200–08. doi:10.1016/S2666-5247(20)30062-8.

Conte D, Fraquelli M, Prati D, Colucci A, Minola E. **Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women**. *Hepatology*. 2000;31(3):751-755.

Dotters-Katz SK, Kuller JA, Hughes BL. Society for Maternal-Fetal Medicine consult series #56: Hepatitis C in pregnancy-updated guidelines: replaces consult number 43, November 2017. *Am J Obstet Gynecol*. 2021;225(3):B8-B18. doi: 10.1016/j.ajog.2021.06.008.

El-Kassas M, Youssif E, Madkour A, Fouad HM, Esmat G, Elbaz T. Outcomes of accidental pregnancy during chronic hepatitis C treatment with direct-acting antiviral agents. *Liver Int*. 2023;43(9):2044-2045. doi: 10.1111/liv.15672.

Fernandez N, Towers CV, Wolfe L, Hennessy MD, Weitz B, Porter S. **Sharing of snorting straws and hepatitis C virus infection in pregnant women**. *Obstet and Gynecol*. 2016;128(2):234-237.

Gervais A, Bacq Y, Bernuau J, et al. **Decrease in serum ALT and increase in serum HCV RNA during pregnancy in women with chronic hepatitis C**. *J Hepatol*. 2000;32(2):293-299.

Hashem M, Jhaveri R, Saleh DA, et al. **Spontaneous viral load decline and subsequent clearance of chronic HCV in postpartum women correlates with favorable IL28B allele**. *Clin Infect Dis*. 2017;65(6):999-1005.

Hattori Y, Orito E, Ohno T, et al. **Loss of hepatitis C virus RNA after parturition in female patients with chronic HCV infection**. *J Med Virol*. 2003;71(2):205-211.

Honegger JR, Kim S, Price AA, et al. **Loss of immune escape mutations during persistent HCV infection in pregnancy enhances replication of vertically transmitted viruses**. *Nat Med*. 2013;19(11):1529-1533.Jhaveri R, Hashem M, El-Kamary SS, et al. **Hepatitis C virus (HCV) vertical transmission in 12-month-old infants born to HCV-infected women and assessment of maternal risk factors**. *Open Forum Infect Dis*. 2015;2(2):ofv089.

Koneru A, Nelson N, Hariri S, et al. **Increased hepatitis C virus (HCV) detection in women of childbearing age and potential risk for vertical transmission - United States and Kentucky, 2011-2014**. *MMWR Morb Mortal Wkly Rep*. 2016;65(28):705-710.

Kuncio DE, E. Newbern C, Fernandez-Viña MH, Herdman B, Johnson CC, Viner KM. **Comparison of risk-based hepatitis C screening and the true seroprevalence in an urban prison system**. *J Urban Health*. 2015;92(2):379-386.

Kuncio DE, E. Newbern C, Johnson CC, Viner KM. **Failure to test and identify perinatally infected children born to hepatitis C virus-infected women**. *Clin Infect Dis*. 2016;62(8):980-985.

Kushner T, Lange M, Sperling R, Dieterich D. Treatment of women with hepatitis C diagnosed in pregnancy: a co-located treatment approach. *Gastroenterology*. 2022;163(5):1454-1456.e1. doi: 10.1053/j.gastro.2022.07.017.

Lin HH, Kao JH. **Hepatitis C virus load during pregnancy and puerperium**. *BJOG*. 2000;107(12):1503-1506.

Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. **Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014**. *Ann of Intern Med*. 2017;166(11):775-782.

Mast EE, Hwang L-Y, Seto DSY, et al. **Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy**. *J Infect Dis*. 2005;192(11):1880-1889.

Owens DK, Davidson KW, Krist AH, et al; US Preventive Services Task Force. **Screening for hepatitis C virus infection in adolescents and adults: US Preventive Services Task Force recommendation statement**. *JAMA*. 2020;323(10):970-975. doi: 10.1001/jama.2020.1123.

Puljic A, Salati J, Doss A, Caughey AB. **Outcomes of pregnancies complicated by liver cirrhosis, portal hypertension, or esophageal varices**. *J Matern Fetal Neonatal Med*. 2016;29(3):506-509.

Resti M, Azzari C, Mannelli F, et al; Tuscany study group on hepatitis C virus infection. **Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1.** *BMJ*. 1998;317(7156):437-441.

Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. **CDC recommendations for hepatitis C screening among adults - United States, 2020**. *MMWR Recomm Rep*. 2020;69(2):1-17.

Shebl FM, El-Kamary SS, Saleh D'aA, et al. **Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages**. *J Med Virol*. 2009;81(6):1024-1031.

Shen GF, Ge CH, Shen W, Liu YH, Huang XY. Association between hepatitis C infection during pregnancy with maternal and neonatal outcomes: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2023;27(8):3475-3488. doi: 10.26355/eurrev_202304_32120.

Tan J, Surti B, Saab S. **Pregnancy and cirrhosis**. *Liver Transpl*. 2008;14(8):1081-1091.

Tasillo A, Eftekhari-Yazdi G, Nolen S, et al. **Short-term effects and long-term cost-effectiveness of universal hepatitis C testing in prenatal care**. *Obstet Gynecol*. 2019;133(2):289-300. doi:10.1097/AOG.0000000000003062.

Waruingi W, Mhanna MJ, Kumar D, Abughali N. **Hepatitis C virus universal screening versus risk based selective screening during pregnancy**. *J Neonatal Perinatal Med*. 2015;8(4):371-378.

Watts T, Stockman L, Martin J, Guilfoyle S, Vergeront JM. **Increased risk for mother-to-infant transmission of hepatitis C virus among Medicaid recipients - Wisconsin, 2011-2015**. *MMWR Morb Mortal Wkly Rep*. 2017;66(42):1136-1139.

Wijarnpreecha K, Thongprayoon C, Sanguankeo A, Upala S, Ungprasert P, Cheungpasitporn W. **Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis**. *Clin Res Hepatol Gastroenterol*. 2017;41(1):39-45.

Yattoo GN, Shafi SM, Dar GA, et al. Safety and efficacy of treatment for chronic hepatitis C during pregnancy: a prospective observational study in Srinagar, India. *Clin Liver Dis (Hoboken)*. 2023;22(4):134-139. doi: 10.1097/CLD.0000000000000082.

Yee LM, Shah SK, Grobman WA, Labellarte PZ, Barrera L, Jhaveri R. Identifying barriers and facilitators of the inclusion of pregnant individuals in hepatitis C treatment programs in the United States. *PLoS One*. 2022;17(11):e0277987. doi: 10.1371/journal.pone.0277987.