Recent Advances in the Epidemiology, Screening, and Management of Hepatitis C Virus Infection in Pregnancy

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Abstract: Hepatitis C virus (HCV) affects an estimated 58 million people worldwide, with rising rates among women of reproductive age. This trend has important implications in pregnancy, as HCV infection can lead to adverse maternal outcomes, mother-to-child transmission, and adverse neonatal outcomes. The perinatal period is a critical time both to identify cases of HCV infection and to initiate treatment, as patients have greater access to care during this time. There has been a guideline shift from risk-based screening for HCV in pregnancy to a universal screening approach. Additionally, several clinical trials are evaluating the use of direct-acting antiviral therapy in pregnancy, with preliminary results demonstrating safety and efficacy. This article discusses the epidemiology of HCV and its implications on pregnancy outcomes, as well as the most recent guidelines on screening and treatment.

Keywords
Hepatitis C virus, pregnancy, mother-to-child transmission, hepatitis C virus screening, antiviral therapy, perinatal outcomes

Hepatitis C virus (HCV) is a global health challenge, with an estimated 58 million people living with chronic infection and approximately 1.5 million new infections each year.[1] The World Health Organization (WHO) set a goal to eliminate HCV infection as a public health threat by 2030 primarily through effective prevention strategies, expanded screening, and timely treatment.[2] However, a 2024 global report on HCV elimination revealed substantial variation by region, with only a minority of countries on track to meet WHO 2030 targets.[3]

Identifying populations at highest risk of HCV infection and transmission patterns by region is essential to successful elimination efforts. In high-income countries, intravenous drug use (IVDU) is the leading cause of transmission, whereas in low-income countries, unsafe medical practices and unscreened blood transfusions remain major contributors.[4] In the United States, the incidence of acute HCV increased 3-fold from 2009 to 2018.[5] Notably, the highest rates were among reproductive-age individuals between 20 and 29 years old, coinciding with the opioid

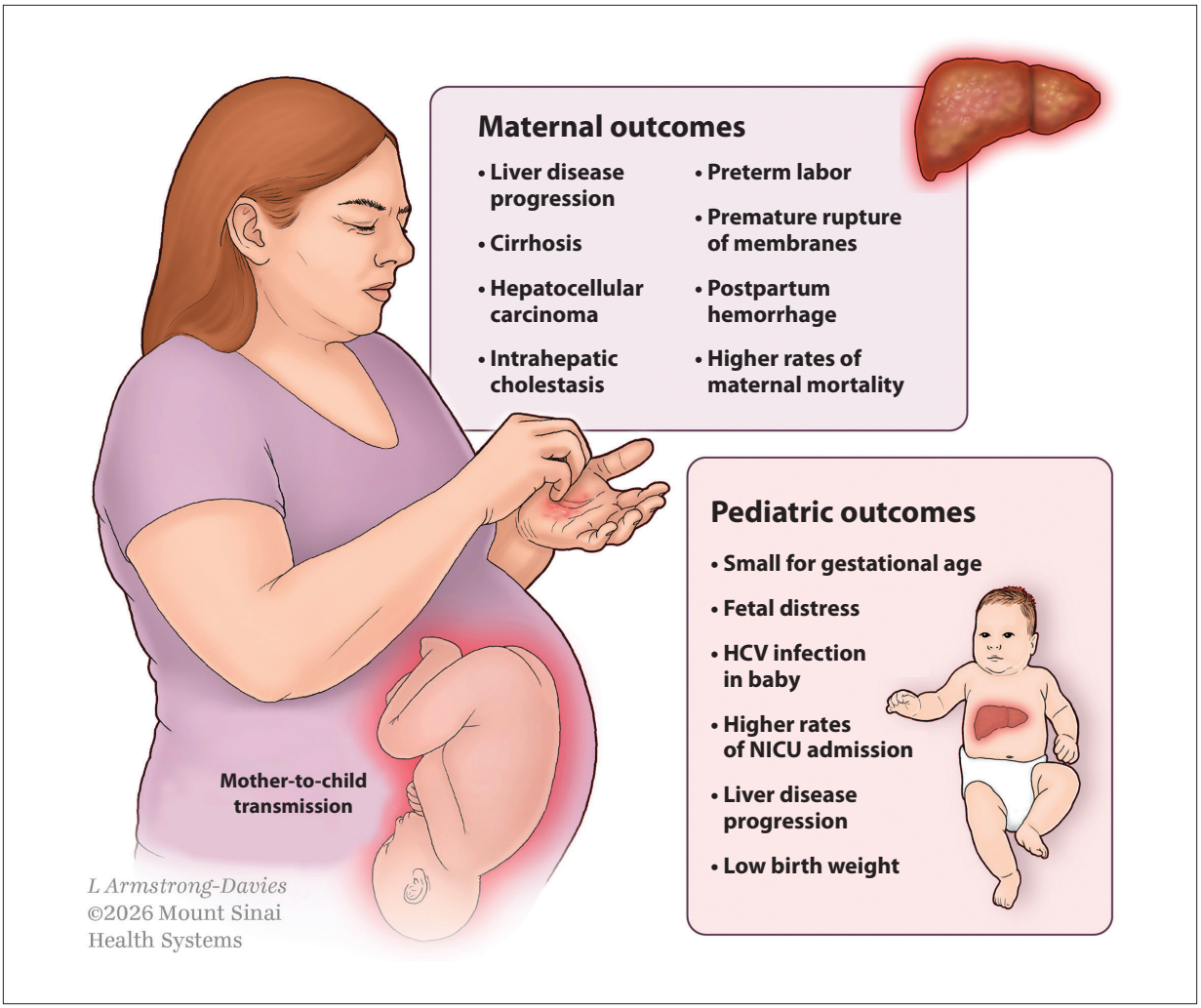

Figure. Maternal and pediatric outcomes in HCV infection.

HCV, hepatitis C virus; NICU, neonatal intensive care unit.

epidemic and increased unsafe IVDU practices.[5,6]

The increase in HCV prevalence among women of reproductive age has important implications, especially in the setting of pregnancy. Key concerns include the risk of mother-to-child transmission (MTCT) and associated outcomes, the impact of HCV infection on maternal and infant health, and the importance of determining appropriate timing of HCV treatment.[7,8] In recognition of these trends, WHO classifies pregnant individuals as a priority population for elimination of HCV, highlighting pregnancy as a critical opportunity for screening and linkage to care.[2] The MTCT terminology is used throughout this article, in line with terminology employed by WHO and the American Association for the Study of Liver Diseases (AASLD).[2,9] This article addresses recent advances in the epidemiology and current management of HCV infection in pregnancy.

Epidemiology of Hepatitis C Virus

In 2019, an estimated 14.9 million women of reproductive age (15-49 years) were living with HCV, accounting for approximately 20% of HCV infections worldwide. China and Pakistan accounted for the greatest absolute number of women living with HCV infection, and the highest prevalence rates were seen in Mongolia and Burundi.[10] Regions with low sociodemographic indexes carry the highest burden of HCV among women of reproductive age. Based on an age-period-cohort analysis of Global Burden of Disease study data, the overall global burden of HCV among women aged 15 to 49 years revealed a downward trend from 1990 to 2021. Although the age-standardized incidence and mortality rates of both acute and chronic HCV infection have declined overall, there was notable regional variability reflecting differences

in health care access and socioeconomic status.[11]

Within the United States, rates of HCV infection have significantly increased among reproductive-age and pregnant women.[5,12,13] A large retrospective cohort study using US National Center for Health Statistics birth records from 2009 to 2017 found that the prevalence of maternal HCV infection rose by 161%, increasing from 1.8 cases to 4.7 cases per 1000 live births.[7] Another large cross-sectional study using the National Inpatient Sample of more than 70 million pregnancies from 1998 to 2018 found a 16-fold rise in HCV-positive pregnancies. Rates reached 5.3 cases per 1000 pregnancies, with the greatest burden in women aged 21 to 30 years.[8] Although estimates vary slightly by data source, all consistently show a marked rise in HCV prevalence among pregnant individuals in the United States.

Demographic factors associated with HCV infection in pregnancy include White or American Indian/Alaska Native race, lower educational attainment (less than 4-year college degree), Medicaid insurance as primary source of payment, and being unmarried.[14] Rates of maternal HCV were higher in nonurban areas compared with large central metropolitan regions, particularly in regions with high rates of IVDU, including Appalachia, Northern New England, the northern border of the Upper Midwest, and New Mexico.[15,16] The uneven distribution of maternal HCV across the United States highlights the need for targeted public health strategies that account for both clinical factors, such as coinfection with HIV, and social determinants of health.

Implications of Hepatitis C Virus Infection on Pregnancy

HCV infection during pregnancy has important implications for both maternal and fetal health. MTCT is the leading cause of HCV infection in children.[17] A 2024 meta-analysis that evaluated MTCT among 28 studies (3838 individuals) found a pooled rate of transmission of 9% in mothers with HCV viremia. The odds of transmission were higher in mothers who had HIV coinfection (odds ratio, 3.1).[18] The major risk factors for MTCT described in the literature include HIV coinfection, HCV RNA greater than 10^6 IU/mL, antepartum vaginal bleeding, prolonged rupture of membranes (>6 hours), episiotomy, and invasive perinatal procedures such as fetal scalp monitoring.[19-22] The mode of delivery (vaginal delivery vs cesarean section) does not affect risk of MTCT, and breastfeeding has not been shown to increase risk of transmission; however, caution is advised if the mother has cracked or bleeding nipples.[23]

The precise timing of MTCT remains incompletely understood.[24] Current estimates rely on the detection of HCV RNA at delivery, such that HCV RNA positivity within 3 days of delivery is suggestive of intrauterine transmission.[25] In a 2005 prospective cohort study of 54 HCV-infected children, 31% tested HCV RNA–positive within the first 3 days of life, consistent with in utero transmission, whereas 50% were initially HCV RNA–negative but tested positive by 3 months, suggesting late intrauterine or peripartum infection.[26] Similarly, a prospective analysis of 1749 children found that approximately 25% of infections occur early in utero, 66% occur later in utero, and 9% occur during delivery.[27] Although limited, available data suggest that the peripartum period, which refers to the period immediately before, during, and after delivery, is the highest risk window for MTCT of HCV.

Maternal HCV infection during pregnancy has been found to increase the risk of adverse outcomes for both the mother and infant (Figure).[22,28] A meta-analysis of 3 studies found that the odds of developing intrahepatic cholestasis of pregnancy (ICP) is 20-fold higher in pregnant women with HCV compared with those without HCV.[29] Another meta-analysis of 9 studies and more than 4 million participants found that the odds of preterm birth are nearly 2-fold higher in pregnancies with HCV,[22,30] consistent with other large studies demonstrating an increased risk of premature rupture of membranes and preterm birth.[31,32] These findings are further confirmed by a large retrospective cohort study in Ontario, Canada using population-based administrative health care data that found an increased risk of ICP, preterm delivery, and postpartum hemorrhage among pregnant individuals who were HCV RNA–positive compared with those with resolved infection.[22] Additionally, a study using data from the 2010 to 2020 National Inpatient Sample found that rates of mortality and cirrhosis were increased among women with HCV during pregnancy.[33] Untreated HCV infection can also lead to liver disease progression and increased risk for hepatocellular carcinoma.[34]

Additionally, HCV infection during pregnancy can lead to MTCT and potential adverse neonatal outcomes, including low birth weight (LBW) and higher rates of neonatal intensive care unit (NICU) admission. A multicenter prospective cohort study found that maternal HCV infection was associated with 2-fold increased odds of NICU admission and 3-fold increased odds of small for gestational age (SGA) birth below the 5th percentile.[35] The higher rates of NICU admission are thought to be partially attributable to increased incidence of SGA. A prospective study in British Columbia, Canada from 2000 to 2003 found that mothers with HCV infection had higher rates of intrauterine fetal death and LBW infants (<2500 g) compared with the general population.[32] These results are consistent with a large meta-analysis consisting

Table 1. HCV Screening Recommendations During Pregnancy by Organization

Organization	Date	Recommendation
AASLD-IDSA	2018	Universal screening for all pregnant individuals[41]
USPSTF	2020	Screening for all adults aged 18 to 79 years, including pregnant adults[42]
CDC	2020	Screening for all pregnant individuals during each pregnancy, except in settings where HCV prevalence <0.1%[43]
ACOG	2021	Screening for all pregnant individuals during each pregnancy[44]
SMFM	2021	Screening for all pregnant individuals during each pregnancy[19]
WHO	2022	Screening in pregnancy in endemic regions or among at-risk individuals[2]
EASL	2023	Screening for all pregnant individuals, ideally at initial presentation for prenatal care[45]
APASL	2024	Establish policies for patient-centered testing guided by recommendations from WHO and national advisory committees[46]

AASLD, American Association for the Study of Liver Diseases; ACOG, American College of Obstetricians and Gynecologists; APASL, Asian Pacific Association for the Study of the Liver; CDC, Centers for Disease Control and Prevention; EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; IDSA, Infectious Diseases Society of America; SMFM, Society for Maternal-Fetal Medicine; USPSTF, US Preventive Services Task Force; WHO, World Health Organization.

of 14 studies (1950-2022) that showed that maternal HCV infection was associated with increased risk of intrauterine growth restriction and LBW.[31] More recently, a retrospective analysis of US Centers for Disease Control and Prevention (CDC) and the Prevention Natality Live Birth Database (2016-2021) further demonstrated increased risk of LBW, NICU admission, congenital anomalies at birth, low 5-minute Apgar scores, neonatal sepsis requiring antibiotics, and need for immediate and prolonged ventilation.[36] Although further research is needed, translational studies suggest that altered placental immune activity in HCV-exposed pregnancies may contribute to these complications.[37]

Screening Guidance for Hepatitis C Virus Infection in Pregnancy

Expert guidelines regarding screening for HCV have evolved from risk-based screening to universal screening over the past several years. In 2012, the CDC recommended that pregnant individuals only be tested for HCV infection if they had known risk factors.[38] Risk factors that would indicate screening include IVDU, HIV-positive status, tattoos or piercings, transplant or blood transfusions prior to 1992, recipient of clotting factors prior to 1987, and long-term hemodialysis.[39] However, studies showed that a risk-based screening protocol was ineffective for capturing individuals who are HCV-positive. For example, a single-center retrospective analysis of pregnant individuals found that among women with known HCV risk factors, 64.1% were not tested, and 10% of women who were found to be HCV-positive had no reported risk factors.[40]

Between 2018 and 2023, guidelines for HCV screening in pregnancy shifted from risk-based to universal screening, beginning with a recommendation from AASLD and the Infectious Diseases Society of America (IDSA).[41] Other organizations, including the US Preventive Services Task Force, CDC, American College of Obstetricians and Gynecologists (ACOG), Society for Maternal-Fetal Medicine (SMFM), WHO, and European Association for the Study of the Liver (EASL), followed suit with updated recommendations for broader screening (Table 1).[2,19,41-46] Current guidelines suggest that all pregnant individuals should undergo an HCV antibody (anti-HCV) test, and those who test positive should also undergo a nucleic acid amplification test for HCV RNA.[47] Ideally, this screening should occur at the first prenatal visit.[48]

The shift to universal screening in pregnancy creates an opportunity to identify cases of HCV infection during a time when people have high contact with the health care system. A universal screening protocol has the potential to improve outcomes for individuals with HCV, reduce pregnancy complications, and identify infants exposed to HCV.[49] Additionally, a study evaluating the cost of testing for HCV with an anti-HCV and an HCV RNA test

Table 2. Summary of Ongoing and Past Clinical Trials on DAAs for HCV in Pregnancy

Authors	Status, year	Trial phase	Number of participants treated	DAAs	Findings
Chappell et al[59]	Complete, 2020	1	9	LDV/SOF	100% cure rate 12 weeks after treatment completion, no infant HCV infections, no safety concerns attributable to treatment
Chappell et al[58]	Complete, 2025	1	10	SOF/VEL	100% cure rate 12 weeks after treatment completion, no infant HCV infections, no safety concerns attributable to treatment, mostly mild adverse effects[a]
Chappell[61]	Ongoing, interim results presented in 2024	4	Goal of 100; 46 completed treatment, 35 achieved SVR	SOF/VEL	100% cure rate 12 weeks after treatment completion, no infant HCV infections, no safety concerns attributable to treatment
IMPAACT Study Group[62]	Site selection completed in 2023	1/2	N/A (goal of 30)	GLE/PIB	N/A

[a]Two participants were lost to follow-up between delivery and 12-week visit. All 8 participants who completed follow-up met the criteria for cure of HCV infection. One participant who was lost to follow-up at week 12 was found to subsequently be cured at a future visit.

DAAs, direct-acting antivirals; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; N/A, not available; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virologic response.

shows that universal screening of HCV during pregnancy is highly cost-effective, with an incremental cost-effectiveness ratio of less than $3000 per quality-adjusted life years gained. Even in states where the prevalence of HCV is very low, the model of universal screening remains cost-effective.[50] Another model similarly found that universal screening was cost-effective and increased identification of infants exposed to HCV at birth from 44% to 92%.[49]

Although there has been a significant increase in the percent of women who are tested for HCV following the implementation of universal screening recommendations, screening is still falling short of universal levels.[51] A recent study that evaluated screening for HCV using data from TriNetX—an electronic health data source from 68 US health care organizations—found that after the change in guidelines, screening increased from 141 to 253 per 1000 person-years. By December 2022, approximately 39% of pregnant individuals had ever been tested for HCV, compared with 90% of pregnant individuals who had ever been tested for HIV.[52] Additionally, individuals with Medicaid are less likely to get tested than those with commercial insurance.[51] Likewise, a 2024 study surveyed physicians who provide prenatal care in the United States and found that among 224 providers, less than half (43%) reported regular use of the ACOG HCV screening recommendation. Physicians who reported that they had general knowledge about HCV and those who reported that screening is easily implemented in their practice were more likely to complete appropriate screening.[53] Further evaluating knowledge gaps among providers, insurance coverage for testing, and integrating HCV testing into the workflow of the first prenatal visit may be helpful for increasing adherence to the updated guidelines.

For children born to mothers with HCV, AASLD guidance has shifted from recommending testing at age 18 months to testing between 2 and 6 months.[41] Earlier testing has been shown to improve health outcomes by facilitating timely diagnosis and follow-up.[54,55] Additionally, earlier testing has the potential to decrease loss to follow-up while reducing anxiety among families who want to know their child's HCV status. Of note, infants should not be tested before they are 2 months of age owing to the risk of false-negative results. As such, the most up-to-date CDC guidelines recommend HCV RNA testing between age 2 and 6 months. Infants with undetectable HCV RNA at or after age 2 months do not require further follow-up, whereas those with detectable HCV RNA should be referred to a specialist for evaluation and treatment.[47] Direct-acting antivirals (DAAs) are currently recommended for all children age 3 years and older with HCV infection, with available options including glecaprevir/pibrentasvir (GLE/PIB; Mavyret, AbbVie), sofosbuvir/velpatasvir (SOF/VEL; Epclusa, Gilead), and ledipasvir/

sofosbuvir (LDV/SOF; Harvoni, Gilead) based on their age and weight.[9,47]

Pregnancy is a critical opportunity to diagnose and link individuals to HCV treatment. This is largely because pregnancy often represents the primary point of contact with the health care system for many individuals, particularly for uninsured or medically underserved populations.[56] As a result, prenatal care often represents the primary entry point for addressing both pregnancy-related and general health care needs.[57] Screening for and identifying HCV in pregnancy allows for counseling about associated pregnancy-related complications, implementation of measures to reduce the risk of MTCT, and linkage to care.

Treatment Considerations

Guidance from various medical associations should be considered when determining treatment for HCV during pregnancy. According to joint AASLD-IDSA guidance, treatment of HCV infection with DAAs is recommended prior to pregnancy to reduce risk of transmission to the fetus.[48] Those who become pregnant while taking DAAs should be counseled about the risks and benefits of continuing with treatment during pregnancy. The lack of robust safety and efficacy data for DAA use during pregnancy has posed a barrier to consensus on treatment guidelines. AASLD and IDSA advise that treatment can be considered on an individual basis through shared decision-making and discussion of the potential risks and benefits to treatment.[48] Likewise, EASL suggests that, if necessary, DAAs can be considered after a thorough discussion among an interdisciplinary team.[45] However, SMFM recommends that DAA therapy only be initiated in the setting of a clinical trial in pregnant individuals.[19,44]

Although there are no US Food and Drug Administration–approved DAAs for the treatment of HCV in pregnancy, emerging data from 2 published phase 1 clinical trials have begun to explore their safety and efficacy (Table 2). The trials studied SOF/VEL in 10 individuals and LDV/SOF in 9 individuals initiated between 23 and 25 weeks of gestation for a 12-week course. Both trials reported a 100% cure rate among participants, no transmission to infants, and no significant safety concerns.[58,59] Among the 10 individuals in the SOF/VEL trial, 1 (8%) participant experienced a grade 3 adverse effect (vomiting) from the medications that led to discontinuation from the trial.[58]

Additionally, the STORC trial is an ongoing multicenter, phase 4 single-arm study of SOF/VEL for treatment of chronic HCV infection during pregnancy.[60] Interim results of the study reveal that 100% of participants (35) had a sustained virologic response at 12 weeks (SVR12). There was no transmission to the fetus, and no significant safety concerns were identified. The most common adverse events attributable to SOF/VEL were nausea and vomiting, fatigue, headache, and gastric reflux.[61] In addition, site selection was completed for the IMPAACT trial, which will be a phase 1/2 trial evaluating the pharmacokinetics and safety of GLE/PIB.[62] Estimated enrollment in this trial is 30 participants at a gestational age of 14 to 32 weeks who will be followed for 12 weeks postpartum.[63] Furthermore, the Treatment in Pregnancy for Hepatitis C (TiP-HepC) registry was established in 2022 to collect real-world data on mother-infant outcomes following DAA exposure during pregnancy.[64] As of June 2025, there have been a total of 37 reported cases of DAA exposure during pregnancy from the United States, Canada, Australia, and Mexico (including 16 cases that were previously not described in published literature).[65] Although obtaining complete data for all cases remains a limitation of the TiP-HepC registry, this platform serves as a centralized repository for safety and efficacy data that can help inform treatment decision-making.

The potential benefits and harms must be carefully weighed when considering DAA use during pregnancy. The greatest limitation is the lack of robust data on DAA use during pregnancy and breastfeeding, highlighting the need for larger studies evaluating safety and efficacy. Additionally, there is still a need for more research on the cost-effectiveness of treatment during pregnancy and achievement of timely access to treatment. Nonetheless, the potential benefits of DAA use during pregnancy should not be underestimated. Treatment can result in maternal cure of HCV, leading to reduced community transmission, perinatal transmission, and HCV-associated complications. Pregnancy may also serve as an opportunity to initiate treatment while individuals with HCV have increased engagement with the health care system and insurance coverage.[66] In a retrospective cohort study of Medicaid-enrolled pregnant individuals with opioid use disorder and HCV, less than 6% of participants had any follow-up visits within 6 months of delivery.[67] These results highlight loss to follow-up among women at risk for HCV and the opportunity to initiate care during the antenatal period.

Despite limited data on DAA use during pregnancy, studies show that individuals with HCV are open to treatment. In a survey of 141 women residing in the San Francisco Bay Area with a history of HCV, 60% reported that they would take antepartum DAAs if such treatment lowered the risk of perinatal transmission. However, only 21% of respondents said that they would take DAAs during pregnancy for the purpose of self-cure, and 20% reported that they would like to see more data on DAAs during pregnancy.[68] These themes have also been observed

in lower-income countries with a high burden of HCV. A study of women in Egypt, Pakistan, and Ukraine found that 544 (88%) would take DAAs during pregnancy, with most reporting they would do so to prevent vertical transmission.[69]

A qualitative analysis of patient and provider attitudes toward DAAs reported that both groups recognized pregnancy as a window of opportunity to initiate treatment given increased insurance coverage and motivation for behavioral change during this period. However, concerns about limited safety data, medication side effects, and cost of the medications were cited as barriers, underscoring the need for more robust studies on the use of DAAs in pregnancy. Obstetricians identified insufficient training, infrequent exposure to HCV in pregnancy, and lack of professional guidelines as additional barriers they face regarding treatment.[70] Real-world data highlight these challenges as well. In a cohort of 23 pregnant individuals with HCV, most were interested in pursuing treatment with DAAs; however, treatment was often delayed owing to insurance approval processes, and many people were lost to follow-up. Although therapy was well tolerated, adherence remained a challenge, as 80% of individuals with HCV completed their course of DAAs, and only 58% presented at their SVR12 visit.[71] These findings emphasize the potential for the use of DAAs during pregnancy while revealing the need for system-level support, such as programs to maximize compliance and improve insurance coverage.

In cases where individuals with HCV are not treated before or during pregnancy, the postpartum period represents another window of opportunity to initiate therapy. Beginning treatment in the postpartum period helps prevent risk of future HCV complications, decrease MTCT in future pregnancies, and reduce risk of further community transmission of the virus. Despite reassuring data on the safety of DAAs during breastfeeding, practice guidance from AASLD and ACOG still discourage the initiation of treatment in breastfeeding individuals.[72,73] A recent study examined the pharmacokinetics of SOF/VEL in 4 breastfeeding individuals and found that the estimated infant dose of these medications was less than 1% of the weight-adjusted daily dose for children.[74] These early results are encouraging and support further study of DAAs in breastfeeding individuals, as this period may be another important opportunity to initiate therapy.

Conclusion

HCV infection during pregnancy presents unique challenges in management and opportunities for intervention and establishment of care. The rising prevalence of HCV among reproductive-age women and potential implications on perinatal outcomes highlight the importance of universal screening in pregnancy. Pregnancy and the postpartum period represent critical periods to identify infection, provide counseling, and initiate treatment, ultimately improving outcomes for individuals with HCV and contributing to population-level HCV elimination goals. Although there are currently no large-scale trials on the use of DAAs during pregnancy, early-phase clinical trials and ongoing studies show promising safety and efficacy. Future directions in this field should focus on establishing the safety and efficacy of DAAs during pregnancy and breastfeeding, as well as optimizing strategies for screening and treatment uptake.

Disclosures

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