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CO-INFECTIONS AND COMORBIDITY (D BHATTACHARYA, SECTION EDITOR)

Evidence for Implementation: HIV/HCV Coinfection and Pregnancy

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Abstract

Purpose of Review In the context of the opioid epidemic, hepatitis C virus (HCV) infection prevalence is increasing among women of reproductive age. Pregnant people with HIV/HCV coinfection may be at increased risk of adverse pregnancy and neonatal outcomes, although research in this key population is lacking.

Recent Findings Treatment with directly acting antivirals (DAAs) has transformed the clinical care for most patients with HCV. However, pregnant people were excluded from trials of these medications. A recent phase I study has shown promise with excellent safety profile for ledipasvir-sofosbuvir; demonstrating no episodes of perinatal transmission, 100% sustained virologic response, and no safety concerns.

Summary Pregnancy represents a time of maximal interaction with the healthcare system and therefore an ideal window of opportunity to cure HCV. Current observational data regarding pregnant people who are co-infected with HCV and HIV suggest poor outcomes such as increased risk of preterm birth; however, there are no prospective and well-controlled studies to fully understand the impact of HIV/HCV coinfection on pregnancy. Phase 1 studies suggest that DAAs are well-tolerated and effective during pregnancy. Only through large, prospective clinical trials will we be able to understand the interaction of HCV and HIV during pregnancy and to evaluate safety and efficacy of DAAs in this key population.

Keywords Perinatal HIV · Perinatal HCV · HIV/HCV coinfection · Directly acting antivirals

Introduction

Human immunodeficiency virus (HIV) serves as a model for the gains that can be achieved through treatment of maternal infection to improve the health of the pregnant person and prevent perinatal transmission. Advances in maternal HIV care have decreased rates of complications such stillbirth, preterm delivery, low birth weight, and small-for-gestational-age infants [1] and have decreased the rate of perinatal HIV infection by > 95% since the 1990s [2]. In this context, hepatitis C virus (HCV) is emerging as an important concern for pregnant people with HIV due to the increasing prevalence of HCV among persons of reproductive age [3–9]. Like HIV, HCV can progress to a chronic infection. Both infections can be transmitted perinatally. However, in contrast to HIV, curative treatment for HCV is available. Despite this, interventions to improve maternal outcomes and reduce perinatal HCV transmission are lacking [10].

Broadly, the development of directly acting antiviral (DAA) medications has transformed the armamentarium for treating HCV infection. These well-tolerated and highly effective medications have been key in reducing the burden of HCV in the general population [11]. However, pregnant people, including those with HIV/HCV coinfection, were excluded from clinical trials and have not been able to access these life-saving medications [12, 13]. This has implications for pregnant individuals with HIV/HCV coinfection which has been associated with poor outcomes such as preterm delivery [14, 15, 16] and increased risk of perinatal transmission of HCV [17].

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Establishing the safety and efficacy of treatment during pregnancy and possible effects on perinatal transmission is important to pregnant people with HIV/HCV coinfection. Treating HCV during pregnancy could capitalize on the high levels of engagement with the healthcare system during the prenatal period and minimize loss to follow-up which has been demonstrated in multiple studies from the (USA) [18, 19, 20]. Treating HCV during pregnancy has many layers of benefits through improving the health of pregnant people, decreasing the burden of HCV for the future generations, and furthering efforts towards HCV elimination. In this article, we describe the current literature surrounding HIV/HCV coinfection during pregnancy, highlight emerging data about safety and efficacy of HCV treatment during pregnancy, and suggest next steps in the research agenda.

Epidemiology

One of the most important impacts of the opioid epidemic is the significant toll it has taken on pregnant people and infants in the US. Injection drug use is a key risk factor for both HIV and HCV, and the opioid crisis has fueled a rise in HCV among women of reproductive age [3–9]. Between 2000 and 2015, the prevalence of HCV among women presenting for delivery in the USA increased significantly, with the highest rate among women with opioid use disorder (216.9 per 1000 live births) [21]. HCV can be transmitted perinatally, consequently increasing prevalence of HCV among pregnant people has implications for the health outcomes of their infants. Notably, the prevalence of HCV among children aged < 2 years old has increased substantially in recent years, and an estimated 1700 infants are born with perinatally acquired annually in the USA [22].

Nationally representative data about prevalence of HCV among pregnant people with HIV the USA are lacking. In 2006, an estimated 3.8% of women with HIV presenting for delivery in New York State were coinfected with HIV and HCV [23]. European studies estimate the prevalence of HIV/HCV coinfection among pregnant people with HIV to be between 2 and 12% [15]. Despite concerns that HIV/HCV coinfection negatively impacts pregnancy outcomes and increases risk of perinatal transmission, there is a dearth of information about the burden of coinfection in this key population.

HIV/HCV Coinfection During Pregnancy

The interaction between HCV infection and pregnancy is not completely understood. Pregnancy is an immune-tolerant state which can hinder the immune control of HCV infection. This can manifest as an increase in HCV ribonucleic acid (RNA) blood levels and decreased liver inflammation [24]. After delivery, the postpartum period can be marked by robust immune reconstitution presenting as acute hepatitis, progression of fibrosis, or spontaneous clearance of HCV [25]. This is possibly due to restoration of functional $CD4^+$ helper T cells during the postpartum period [26]. HIV/HCV coinfection might temper these postpartum HCV outcomes, given that HIV disease affects CD4 + helper T cell number and function. However, there are no studies characterizing the impact of HIV/HCV coinfection on HCV disease severity or the rate of spontaneous clearance of HCV infection in the perinatal period.

The impact of HCV on pregnancy outcomes is also controversial. Some experts believe that obstetric outcomes for pregnant people with HCV are roughly equivalent to outcomes for uninfected women in the absence of cirrhosis [27]. However, multiple studies suggest that there is likely some negative impact on pregnancy. An Italian cohort of 45,000 individuals screened for HCV during pregnancy found that intrahepatic cholestasis of pregnancy was 10 times higher among those who screened positive for HCV and that gestational diabetes was twice as likely in this group [28]. Another meta-analysis including three large studies of pregnant people with HCV monoinfection showed an increased risk of intrahepatic cholestasis of pregnancy (pooled odds ratio [OR] 20.40, (95% confidence interval [CI]: 9.39–44.33, $I^2 = 55\%$) [29]. American Association for Study of the Liver/Infectious Diseases Society of America (AASLD/IDSA) HCV Guidance recommends that clinicians should have a high degree of suspicion for intrahepatic cholestasis of pregnancy among pregnant people with HCV infection who present with jaundice or pruritis. In this instance, there should be assessment of liver enzymes and serum bile acids [30]. Fetal complications have also been described and include preterm delivery, intrauterine growth restriction, admission to the neonatal intensive care unit, low birth weight, and congenital anomalies [31, 32]. However, these studies are not well-controlled for confounding variables such as tobacco, alcohol, or other substance use which might also mediate such outcomes.

In considering HIV/HCV coinfection, three observational studies from Europe suggest increased risk of preterm delivery. In an Italian cohort of 105 women from 2001 to 2015, coinfection with HIV/HCV was shown to be associated with an increased risk of preterm delivery, occurring in 41% of births. Most women were on antiretroviral therapy (ART) at the time of conception; however, only about one-third entered pregnancy with an undetectable viral load [14]. Increased risk of preterm delivery was corroborated in a French study using data from the French Perinatal Cohort from between the years of 2005 and 2013. In this study of 4236 pregnant people with HIV, HIV/HCV prevalence was found to be 1.7%. When comparing pregnant people who were mono-infected with HIV and those who were coinfected with HIV and HCV, coinfection

was associated with higher risk of preterm delivery with an adjusted OR of 3.0 (95% CI: 1.6–5.7, $p < 0.001$) and cholestasis with an adjusted OR of 4.1 (95% CI: 1.5–10.8, $p = 0.005$). Notably, only about half of the HIV/HCV coinfected cohort had virologic control of HIV [15]. Lastly, a study of 339 HIV/HCV coinfected pregnant people from Spain collected from 2000 to 2012 demonstrated a 50% rate of preterm delivery. This cohort, which included data from 2000 to 2012, had > 90% access to ART during pregnancy with a median viral load of 50 copies/mL (15–200) at delivery [16].

These observational studies from Europe suggest that HIV/HCV coinfection may be associated with a dramatically high rate of preterm birth. However, they include a population with heterogeneous uptake of ART which likely impacts clinical outcomes. The study designs are retrospective with the inherent limitations of possible missing data, bias due to confounding, and inability to establish a causal relationship between HCV and outcomes. Lastly, it is unclear how generalizable these data are to the US population.

Perinatal Transmission and Significance for Pediatric Populations

The understanding of perinatal transmission and spontaneous clearance among perinatally infected children has been evolving as new data have emerged, and transmission may be more common than previously realized. It has generally been accepted that perinatal transmission occurs in 5–6% of pregnancies when the mother is infected with HCV. A 2014 meta-analysis showed that perinatal transmission occurred in 5.8% of infants born to mothers with HCV infection, and 10.8% to mothers who are HIV/HCV coinfected [17]. Recently, Ades et al. re-analyzed data from more than 1700 children born to mothers with HCV mono-infection from three prospective cohorts. This analysis revealed that perinatal transmission rates were higher than previously reported: 7.2% (95% CI: 5.6–8.9%) in mothers who were HCV mono-infected and 12.1% (95% CI: 8.6–16.8%) in HIV/HCV co-infected women. The increased risk of perinatal transmission among pregnant people with HIV/HCV coinfection is not fully understood; however, it is possible that it may be due to higher HCV RNA viral loads because of HIV-mediated immunosuppression in the absence of ART [33, 34].

It is important to note that studies depicting an increased the risk of perinatal transmission of HCV for pregnant people who are HIV/HCV coinfected include data from before the current ART era, when people were more likely to be immunocompromised from HIV infection during pregnancy. An Italian cohort of HIV/HCV co-infected pregnant people with access to ART during pregnancy demonstrated that the perinatal transmission rate of HCV was similar to HIV-uninfected population (7.0%, 95%CI: 3.7–10.4%) [16]. Another study of 155 children born to individuals with HCV infection, 15 of whom had HIV/HCV coinfection, showed similar levels of HCV viremia between HCV-mono-infected and HIV/HCV coinfected pregnant people. There was also no increase in transmission among those with HCV/HIV coinfection—notably all study individuals had access to ART [35]. These studies support the concept that any increase in perinatal transmission among HIV/HCV coinfected individuals might be driven by HIV-mediated immunosuppression, and that access to ART might mitigate this risk.

Despite growing knowledge regarding the risks of perinatal transmission, the true burden of perinatally acquired HCV remains unknown. There are clear guidelines from the IDSA/AASLD recommending that HCV-exposed infants receive an HCV antibody test after 18 months of age or HCV RNA test after 2 months old [36]; however, multiple studies evaluating healthcare utilization have shown that HCV-exposed infants are not routinely linked to testing for HCV [18,37–42]. For example, a recent study from a large health center estimated that at least two-thirds of perinatally acquired HCV cases were missed due to lack of recognition of risk factors and inconsistencies in documenting maternal infection in the child's medical record [37]. This could be due to the complicated algorithm with testing long after birth for diagnosing perinatally acquired HCV. Because maternal HCV immunoglobin G antibodies are passively transferred via the placenta while in utero, diagnosing perinatally acquired HCV requires a complex algorithm with precise timing. Currently, it is recommended that infants at risk for perinatal transmission are tested with an antibody test at 18 months [36]. If positive at that time, they are presumed infected. Subsequently, if a child is diagnosed with HCV, it is recommended that the child be followed to 3 years of age and then tested with HCV RNA assay to confirm chronic infection. If they remain infected, they should be treated with DAAs. These highly effective and well-tolerated therapies have been approved for children as young as 3 years old [36]. Missed opportunities to identify and treat children living with HCV can lead to preventable health consequences such as lower quality of life, cirrhosis, hepatocellular carcinoma, and risk of liver-related mortality [41, 43–47]. Testing of infants as early as 2 months of age with HCV RNA test could reduce the significant gaps in HCV testing among infant that are perinatally exposed, which is a more efficient method identify children with perinatal HCV [48]. Ideally, preventing perinatal transmission upstream through treatment of pregnant people with HCV could obviate this complicated algorithm for diagnosing and treating perinatally acquired HCV with dual gains to the mother and child.

HCV Screening for Pregnant People Living with HIV

Given increases in prevalence of HCV among women of reproductive age, AASLD/IDSA recommended universal screening of all pregnant individuals in 2018 (27). This recommendation was eventually taken up by both the US Preventive Task Force (USPSTF) and Centers for Disease Control (CDC) in 2020 (5, 6). Most recently, the American College of Obstetricians and Gynecologists (ACOG) issued a Practice Advisory in May 2021 in concordance with the CDC and USPSTF guidance to recommend universal screening during pregnancy [49]. In light of these changing guidelines, uptake of testing has not been ubiquitous, but it has increased steadily over time. A study of over 5 million pregnant persons showed that the percentage of individuals with a prenatal HCV screening test has increased from 16.6% in 2011 to 40.6% in 2021 [50].

All pregnant people living with HIV should have been screened upon entry into HIV care and linked to treatment with DAAs [51]. Ideally, treatment of HCV among those coinfected with HIV and HCV would occur prior to pregnancy. However, one study of almost 30,000 people living with HIV showed that 77.9% had been screened for HCV and only 17.8% of eligible individuals had initiated treatment with DAAs. [52] Given that most individuals living with HIV who are eligible for HCV treatment are not linked to care, guidelines recommend screening for HCV among all individuals with HIV who are pregnant per the recommendation for the general population [53].

Screening for HCV during pregnancy is crucial to identify persons with HIV/HCV coinfection, so they can be offered HCV treatment after delivery. Knowledge of maternal HCV infection is also the first step necessary to identify infants who have been exposed to HCV and might be at risk perinatal transmission. Lastly, because HIV/HCV coinfection has been associated with adverse outcomes such as preterm birth, knowledge of HIV/HCV coinfection guides strategies for monitoring for these outcomes.

Current Recommendations for Management of HIV/HCV Coinfection During Pregnancy

Caring for a pregnant person with HIV/HCV coinfection is complex, and data are limited regarding the optimal care during pregnancy. Once HIV/HCV coinfection has been established, consultation with an expert in HIV and HCV is strongly recommended by current guidelines [53].

Regarding management of HIV, there are no data to support alternative ART regimens for HIV/HCV coinfection from those recommended for HIV monoinfection during pregnancy. Ensuring that pregnant people are on appropriate ART is crucial to reduce complications of HIV disease in the mother and reduce perinatal transmission [53]. It is possible that HIV/HCV coinfection impacts virologic suppression of HIV. One study of 318 pregnant women with HIV on ART in Canada showed that HCV was associated with virologic rebound of HIV near delivery [54]. It is unclear if coinfection predisposes pregnant people to HIV virologic escape, or if concomitant behavioral risk factors such as low medication adherence and substance use within the study population might have accounted for this finding. HIV viral load should be monitored monthly if RNA levels are detectable. Once HIV RNA levels are undetectable, a patient's viral load should be assessed every 3 months during pregnancy at a minimum [53].

Monitoring of pregnant patients with HIV/HCV coinfection also includes evaluation of transaminases at 3-month intervals during pregnancy given concerns regarding concurrent liver injury from HCV infection and drug toxicity from ART. This recommendation is informed by studies showing liver enzyme elevation among pregnant people with HIV mono-infection; however, this trend was observed among patients on nevirapine and protease inhibitors such as lopinavir [55]. These medications are no longer preferred in pregnancy. Generally, the integrase inhibitors dolutegravir or raltegravir are recommended as a component of ART during pregnancy. However, there are no studies evaluating the trend of liver enzymes during pregnancy in the integrase inhibitor era to inform monitoring guidelines. Additionally, because HIV/HCV coinfection is also associated with elevated risk of intrahepatic cholestasis of pregnancy, beyond the increased risk conferred by HCV mono-infection, close monitoring of liver enzymes among pregnant people with HIV/HCV coinfection is recommended [29, 53].

There has been some interest in scheduled cesarean for decreasing the risk of perinatal transmission of HCV. The USPSTF reviewed the existing evidence regarding any association between mode of delivery (caesarian or vaginal birth) on risk of transmission from 6 studies. The analysis included 3025 pregnant people. No studies showed a statistically significant association between mode of delivery and risk of perinatal transmission of HCV [56]. Therefore, the recommendations for mode of delivery for pregnant people with HIV/HCV coinfection do not differ from those with HIV infection alone [53].

Duration of membrane rupture and use of invasive fetal monitoring have also been suggested as a modifiable risk factor for transmission of HCV. However, data are limited. In a study of 189 pregnant people with HCV, membrane rupture of greater than 6 h (adjusted OR 9.3, 95% CI: 1.5–179.7) and invasive fetal monitoring (adjusted OR

6.7, 95% CI: 1.1–35.9) were associated with increased risk of perinatally acquired HCV in the infant [57]. Given the small size of this study, more data are needed to better estimate the impact of prolonged rupture of membranes and invasive fetal monitoring on risk of HCV transmission. In the absence of reassuring data, ACOG and the US Society for Maternal–Fetal Medicine recommend avoiding invasive fetal monitoring, episiotomy, use of operative delivery, and prolonged rupture of membranes during labor [58].

Breastfeeding has not been shown to be associated with transmission of HCV. A large study of nearly 3000 patients from 14 cohort studies showed no association between breastfeeding and HCV transmission. Breastfeeding is recommended for pregnant people with HCV mono-infection in the absence of cracked nipples [53]. Because HCV does not contribute to increased transmission risk, recommendations surrounding breastfeeding for people with HIV/HCV coinfection do not differ from recommendations for people with HIV mono-infection.

There is considerable interest regarding treatment during pregnancy and how this might mitigate the risk of HCV transmission. Because HCV RNA levels in perinatally infected infants often become detectable only several weeks after birth, it has been suggested that transmission mostly occurs intrapartum [59]. This raises the possibility of using DAAs to eradicate infection during pregnancy, so a pregnant person is not viremic at birth. One recent report demonstrated no episodes of perinatal transmission when treated with ledipasvir-sofosbuvir during the second trimester, supporting this idea [60••]. Despite growing momentum, treatment is not currently recommended during pregnancy, and more evidence is needed in this area.

Potential for Treatment

DAAs offer very simple, oral, once daily dosing that achieve SVR of greater than 95% in nearly all patient groups [61, 62]. New pan-genotypic regimens can be used to treat patients with comorbidities that previously complicated HCV treatment such as cirrhosis and history of prior treatment exposure. Given these novel medications, decision-making surrounding HCV treatment is becoming less complex.

The development of DAAs has raised the possibility of treating during pregnancy to cure a pregnant person of HCV and to prevent perinatal transmission [25]. However, treatment is not offered during pregnancy because pregnant people were excluded from trials of DAAs [10].

In considering the possibility of treating HCV during pregnancy, there are many factors to consider. Benefits of treatment during pregnancy include the possibility of reducing perinatal transmission of HCV and potential to decrease HCV-associated adverse pregnancy outcomes, although these need to be studied further. Practically, pregnancy represents a window of opportunity when many mothers have guaranteed health insurance and regularly scheduled prenatal visits. Currently, curing HCV in pregnant people relies upon referral for treatment after delivery. Yet, studies have shown poor rates of follow-up during this vulnerable time [18, 19]. Treating during pregnancy could overcome this barrier. There is emerging data to suggest that treatment during pregnancy might be safe and effective. In a recent pharmacokinetic study of 9 pregnant women who began treatment with ledipasvir-sofosbuvir at 23–24 weeks of gestation, all maternal participants were cured of HCV, none of the infants acquired HCV perinatally, and no pharmacokinetic or safety concerns were noted [60••]. However, larger studies with pan-genotypic regimens are needed.

Next Steps

In contrast to management of HIV during pregnancy, which is an established public health priority, HCV among pregnant people is just emerging as a public health concern. Epidemiologic data demonstrate that HCV prevalence is increasing in the context of the opioid epidemic; however, no new data have been published to evaluate the trends in HIV/HCV coinfection in this key population. Also, HCV infection can have an impact on the health of the pregnant person living with HIV. Observational studies from Europe suggest that HIV/HCV coinfection is associated with preterm delivery and increased risk of cholestasis of pregnancy beyond that conferred by HCV infection alone. Future research must include high quality, well-controlled, and prospective studies of people who are HIV/HCV coinfected to characterize the effect of coinfection on obstetric outcomes, fetal outcomes, and perinatal transmission. These estimates will also be useful to determine the safety and efficacy of DAA treatment during pregnancy for people with HIV/HCV.

Data are desperately needed regarding exposures of DAAs during pregnancy. To date, there is a small pharmacokinetic study of ledipasvir/sofosbuvir and several other case series describing DAA treatment in pregnancy [60••,63–65]. To add to these data, the Coalition for Global Hepatitis Elimination launched the Treatment In Pregnancy for Hepatitis C (The TiP-HepC) Registry to collect clinical information with the goal of prospectively informing decision-making for treatment of HCV during pregnancy [66]. This registry will provide safety data regarding exposures in the first trimester, which will not be available from prospective clinical trials. However, registries are limited as data could be missing, or poor outcomes might be over-reported; thus, prospective trials are necessary to fill those data gaps. Though data on DAA treatment during pregnancy remains

scant at this moment, there are no safety concerns identified to date regarding DAA treatment during pregnancy. There are currently two trials underway: (1) a small pharmacokinetic study of sofosbuvir/velpatasvir in pregnancy which has recently completed enrollment (NCT04382404) and (2) a large multi-center study of the safety and efficacy of sofosbuvir/velpatasvir treatment during pregnancy (NCT05140941).

There needs to be a paradigm shift in the research community's approach to studying interventions important to pregnant people. This was poignantly highlighted to world in the context of the COVID-19 pandemic during which pregnant people were excluded from studies of the messenger RNA (mRNA) vaccines for SARS-CoV2 despite recognition that pregnant people were vulnerable to COVID-related illness and death [67]. Because of this, pregnant people and their healthcare providers were forced to forge ahead, attempting to weigh the mounting evidence suggesting elevated risks of complications from COVID-19 infection and the unknown safety profile of vaccination. This untenable situation could have been avoided. Moving forward, in the absence of concerns specific to pregnancy, pharmacokinetic studies should be initiated in the pregnant population during drug developing after dosing in non-pregnant individuals has been established [68]. For drugs that would have beneficial health impacts during pregnancy (like HCV DAAs), randomized-controlled trials should not exclude pregnant people by default. Rather than protecting pregnant people *from* research, we can protect them *through* research. The first HCV DAAs were FDA-approved in 2015; however, the first pharmacokinetic study of these antivirals in pregnancy was published in 2020. Despite ample data regarding the pharmacokinetic interactions between DAAs and ART in the general population with HIV/HCV coinfection, there have been no studies evaluating important drug interactions during pregnancy when pharmacokinetics are impacted by physiologic changes [69–71]. We must chart a path forward that includes rigorous evaluation of the safety and efficacy of interventions important to pregnancy. This is particularly important to our patients with HIV/HCV coinfection. However, we continue to miss the mark.

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Declarations

Competing interests Dr. Chappell has received research support and served on advisory boards for Gilead Sciences. Dr. Curtis declares no competing interests.

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•• Of major importance

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