Considering direct-acting antivirals to cure hepatitis C virus during pregnancy: is this the last treatment frontier?

Ther Adv Infectious Dis

2019, Vol. 6: 1–4

DOI: 10.1177/2049936119838229

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Hepatitis C (HCV) is on the rise among women of childbearing age as well as young children in the USA, suggesting increasing mother-to-child transmission (MTCT) of the virus.[1] Epidemiologic data demonstrates that HCV is now a bimodal disease. In addition to the originally identified birth cohort (1945–1965), a second spike in prevalence is recognized in individuals between the ages of 20 years and 35 years, driven primarily by the concurrent rise in injectable opioid abuse, as well as ongoing challenges to HCV prevention and access to HCV direct-acting antiviral (DAA) treatment.[2,3] This younger demographic includes women of reproductive age in the USA where the number of exposed women doubled between 2006 and 2014. As a result, rates of HCV among pregnant women at delivery increased 89% between 2009 and 2014. HCV infection in infants and children has also increased, presumably as a result of MTCT of the virus.[4,5]

In reaction to the increasing prevalence of HCV among women and children, the American Association For The Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA) guidelines recently updated their recommendations to include universal, rather than risk-based, HCV screening among pregnant women.[6] As expected, more women are now being diagnosed with HCV in pregnancy. This poses a clinical dilemma as therapeutic options to interrupt MTCT are limited. Moreover, liver and obstetric national societal guidelines discourage the use of antiviral HCV therapy during pregnancy despite existing algorithms for the use of antiviral therapy to disrupt transmission in other viral infections such as hepatitis B virus (HBV) and HIV. Still, the use of DAA therapy during pregnancy is potentially attractive on many levels.

Here, we discuss several reasons to consider DAA therapy during pregnancy.

(1) Clinicians are encountering more HCV during pregnancy as rates of HCV in this demographic have increased dramatically.

State data confirms an astonishing increase of HCV. In Ohio, between 2006 and 2015, the rate of pregnant women infected with HCV increased by 631%, with 0.5% of all live births being to HCV+ women[7] In Kentucky the rate increased over 200% between 2011 and 2014, with 1.6% of live births being to HCV+ women[8] while in Tennessee the rate increased 89%. Currently 2.3% of births in West Virginia are to HCV+ women.[5]

Nationally, HCV rates during pregnancy have increased by significantly more than those of HBV or HIV and national birth certificate data have demonstrated an increase of 68% in the proportion of infants born to mothers with HCV.[8,9] Given these increases in HCV, there will be more women potentially seeking treatment for HCV during pregnancy.

(2) Identification of perinatally transmitted HCV is poor as children born to mothers infected with HCV are rarely tested.

The rate of HCV vertical transmission is generally accepted to be around 5.8% [95% confidence interval (CI) 4.2–7.8%] in women with HCV and about 10.8% (95% CI 7.6–15.2%) among HIV/HCV co-infection.[10] However, the true rate of MTCT is difficult to ascertain as few infants are appropriately tested. For example, between 2011 and 2013, only 16% of children born to HCV+ women in Philadelphia had appropriate testing.

Between 2006 and 2014 in Pittsburgh, only 31% of children with perinatal HCV exposure received any well-child services with only 30% receiving appropriate HCV screening.[11,12]

Even if these estimates of MTCT are correct, transmission rates of HCV are in the same range as the rate of MTCT in highly viremic women with HBV (despite birth dose HBV vaccination and hepatitis B immunoglobulin).[13] Here, guidelines universally recommend antiviral therapy in the third trimester purely to disrupt the risk of MTCT of HBV. This short course of therapy offers no benefit to the mother and may even increase the risk of postpartum flare when therapy is discontinued.[14] Treating HCV during pregnancy would not only cure disease in the mother, but also potentially lower the risk of MTCT.

(3) Pediatric HCV has increased in concert with the increase of maternal HCV.

Childhood HCV is increasing with MTCT as the leading cause for pediatric infection. During the past decade, the prevalence of HCV infection in young children throughout the USA has increased more than three-fold, increasing from 0.5% to 1.6%.[1] Also during this time, the rate of infant HCV referrals in parts of Appalachia (southern Ohio and western Pennsylvania) has increased more than four-fold. Furthermore, between 2006 and 2012, the number of hospitalizations of children infected with HCV increased 37%, to 3.7 per 10,000 admissions.[15,16]

(4) Treatment during pregnancy is an attractive option from the perspective of both mother and child.

Unfortunately, even after appropriate diagnosis, many persons in need of therapy are unable to receive it. While specific data on pediatric HCV are limited, overall linkage rates are poor. In a single center in Tennessee (representative of among the most affected demographics) only 60% of those identified with HCV were able to begin treatment, while in Philadelphia only 62% were able to follow up with an appropriate subspecialist for treatment.[17,18]

Although all oral treatment options are expanding to the pediatric population, identification and linkage to care and timing of therapy remain problematic. Untreated, these children can both be stigmatized as well as at risk for viral transmission to others. Furthermore, a recent study by the UK HCV Research Group found that children who are infected with HCV through MTCT developed cirrhosis at an earlier age than children who acquired infection through other routes during childhood, and are also at risk of acquiring hepatocellular carcinoma,[19] increasing the importance of interrupting MTCT. Moreover, when surveyed, the majority of women with a history of HCV appear to be interested in HCV treatment during pregnancy if it could decrease MTCT.[20]

Although those opposed to treatment during pregnancy advocate for treatment postdelivery, linkage to care postdelivery is difficult. Pregnancy offers a period when high-risk women have access to health care. Postpartum, women (and infants) are often lost to follow up.[12] Furthermore, there are significant gaps in the cascade of care at the linkage phase, even in highly specialized settings such as obstetric clinics for women with substance use disorders.[21] Treatment of HCV during pregnancy would reduce loss to follow up by treating women at a time when they are engaged in their pregnancy care.

Despite these reasons to consider treatment during pregnancy, many providers are hesitant, citing potential risk to the infant of drug exposure and insufficient benefit to the mother to outweigh these risks. However, *in vitro* studies suggest DAA drugs are safe during pregnancy.[22] Sofosbuvir, a main stay of multiple DAA regimens, appears to have a favorable pharmacokinetic profile that should not be affected by pregnancy and no negative pregnancy outcomes have been reported in a registry of the European Medical Agency.[23] Although for US Food and Drug Administration (FDA) approval, evaluation of medications in pregnancy is not required (and most medications are used 'off-label' during pregnancy), preclinical studies of pregnant rats and rabbits showed there were no safety concerns for antenatal administration, which was what informed the pregnancy category B designation of many DAA regimens. Since 2014, other DAAs, such as sofosbuvir and velpatasvir, and glecaprevir/pibrentasvir, have been approved and none of these medications have been known to cause any fetal toxicities in preclinical studies except when the dose was high enough to produce maternal toxicity as well.[24–26] Interestingly providers are generally comfortable with treating HBV during pregnancy, despite arguably the lesser benefit to the mother and

potential risks of drug exposure to the infant, even though HBV treatment does not provide cure and leads to a risk of HBV flare following discontinuation of HBV therapy postpartum.[27]

Studies are underway to confirm the efficacy of DAA therapy given during pregnancy, both in curing the mother and disrupting MTCT. Registries and clinical trials to evaluate further the use of DAAs in the pregnancy period will be important to further clarify safety and efficacy. Future studies will also need to identify maternal and fetal factors that may make treatment during pregnancy optimal over postpartum therapy, which take into consideration the safety of DAA treatments, an individual's particular risk of loss to follow up postdelivery, and the likelihood of potential treatment of their children in the event of MTCT. Lastly, engaging the obstetrician and patient in this conversation is vital. However there is no conversation if there are no options.

Funding

NR and JC received grant support from Gilead.

Conflict of interest statement

TK has an advisory role for Gilead. NR has an advisory role for AbbVie, Gilead and Merck.

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References

1. Ly KN, Jiles RB, Teshale EH, *et al*. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. *Ann Intern Med* 2017; 166: 775–782.
2. Centers for Disease Control and Prevention. Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002–2009. *MMWR Morb Mortal Wkly Rep* 2011; 60: 537–541.
3. Page K, Morris MD, Hahn JA, *et al*. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clin Infect Dis* 2013; 57(Suppl. 2): S32–S38.
4. Ly A, Cheng HH and Alwan L. Hepatitis C infection and chemotherapy toxicity. *J Oncol Pharm Pract* 2019; 25: 474–480. Epub ahead of print 11 October 2017. doi: 10.1177/1078155217734626
5. Patrick SW, Bauer AM, Warren MD, *et al*. Hepatitis C virus infection among women giving birth – Tennessee and United States, 2009–2014. *MMWR Morb Mortal Wkly Rep* 2017; 66: 470–473.
6. AASLD-IDSA. Recommendations for testing, managing and treating hepatitis C, http://www.hcvguidelines.org (2018, accessed 7 December 2018).
7. Rossi RM and Warshak CR. Prevalence of maternal hepatitis C virus infection in Ohio. *Obstet Gynecol* 2018; 132: 708–716.
8. 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: 705–710.
9. Salemi JL, Spooner KK, Mejia de Grubb MC, *et al*. National trends of hepatitis B and C during pregnancy across sociodemographic, behavioral, and clinical factors, United States, 1998–2011. *J Med Virol* 2017; 89: 1025–1032.
10. Benova L, Mohamoud YA, Calvert C, *et al*. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis* 2014; 59: 765–773.
11. Kuncio DE, Newbern EC, Johnson CC, *et al*. Failure to test and identify perinatally infected children born to hepatitis C virus-infected women. *Clin Infect Dis* 2016; 62: 980–985.
12. Chappell CA, Hillier SL, Crowe D, *et al*. Hepatitis C virus screening among children exposed during pregnancy. [Published online ahead of print May 2, 2018]. *Pediatri* doi:10.1542/peds.2017-3273.
13. Barritt AS and Jhaveri R. Treatment of hepatitis C during pregnancy – weighing the risks and benefits in contrast to HIV. *Curr HIV/AIDS Rep* 2018; 15: 155–161.
14. Terrault NA, Lok ASF, McMahon BJ, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; 67: 1560–1599.
15. Squires JE and Balistreri WF. Hepatitis C virus infection in children and adolescents. *Hepatol Commun* 2017; 1: 87–98.
16. Barritt AS, Lee B, Runge T, *et al*. Increasing prevalence of hepatitis C among hospitalized children is associated with an increase in substance abuse. *J Pediatr* 2018; 192: 159–164.
17. Zuckerman A, Douglas A, Nwosu S, *et al*. Increasing success and evolving barriers in the

hepatitis C cascade of care during the direct acting antiviral era. *PLoS One* 2018; 13: e0199174.

18. Coyle C, Viner K, Hughes E, *et al*. Identification and linkage to care of HCV-infected persons in five health centers – Philadelphia, Pennsylvania, 2012–2014. *MMWR Morb Mortal Wkly Rep* 2015; 64: 459–463.
19. Modin L, Arshad A, Wilkes B, *et al*. Epidemiology and natural history of hepatitis C virus infection among children and young people. *J Hepatol* 2019; 70: 371–378.
20. Kushner T, Cohen J, Tien PC, *et al*. Evaluating women's preferences for hepatitis C treatment during pregnancy. *Hepatol Commun* 2018; 2: 1306–1310.
21. Epstein RL, Sabharwal V, Wachman EM, *et al*. Perinatal transmission of hepatitis C virus: defining the cascade of care. *J Pediatr* 2018; 203: 34–40.e1.
22. Kanninen TT, Dieterich D and Asciutti S. HCV vertical transmission in pregnancy: new horizons in the era of DAAs. *Hepatology* 2015; 62: 1656–1658.
23. Spera AM, Eldin TK, Tosone G, *et al*. Antiviral therapy for hepatitis C: has anything changed for pregnant/lactating women? *World J Hepatol* 2016; 8: 557–565.
24. Food and Drug Administration. *Harvoni* [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205834s017lbl.pdf
25. Food and Drug Administration. *Epclusa* [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208341s000lbl.pdf (accessed 15 January 2019).
26. Food and Drug Administration. *Mavyret* [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209394s000lbl.pdf (accessed 8 February 2018).
27. Chang CY, Aziz N, Poongkunran M, *et al*. Serum aminotransferase flares in pregnant and postpartum women with current or prior treatment for chronic hepatitis B. *J Clin Gastroenterol* 2018; 52: 255–261.