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Hepatitis C in Pregnant Women and Their Children

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Abstract

Hepatitis C virus (HCV) infection presents unique challenges in the setting of pregnancy. HCV can contribute to pregnancy-related morbidity and pregnancy can influence the course of HCV infection. There is a significant risk of transmission to the fetus and newborn infant. Identification of HCV infection in women of childbearing potential and those who are currently pregnant offers important opportunities for the woman and for past, present and future children.

Introduction

Infection with hepatitis C virus (HCV) is common in women of childbearing potential, having doubled between 2006 and 2014. This increase is due in large part to the opioid epidemic and injection drug use (IDU). Currently, 1-2.5% of women in the peak childbearing age range have HCV, with wide geographical variation in the United States.[1] The State of Delaware has recently sought to identify infected pregnant women through use of the hepatitis C registry. Through 2014, about 29,000 infected women gave birth each year in the U.S., and that number is expected to increase.[2] Currently, it is estimated that 132,000 U.S. children and adolescents have HCV. In developed countries with hepatitis B virus (HBV) immunization programs, HCV has become the most common cause of chronic hepatitis in children.[3]

Caring for women of childbearing potential who are infected with HCV has challenges. They often are young, un- or under-insured, and currently or formerly addicted to opioids and other substances. Paradoxically, independent of access and linkage to care, this group is often considered “easy to treat,” in that most have been infected less than five years, have minimal hepatic fibrosis, and have fewer co-morbidities. Pregnancy is a time of potential opportunity for engaging women in HCV care, as they are usually seeking prenatal services and may be more likely to have insurance coverage.

Pregnancy has an effect on the course of HCV and vice versa. HCV RNA levels rise during the first and third trimesters and transaminase levels tend to fall at those times. Women with HCV also have higher rates of intrahepatic cholestasis of pregnancy. Currently, antiviral therapy during pregnancy is not recommended since the safety and efficacy of direct-acting antivirals (DAAs) in pregnancy have not been established (ribavirin is contraindicated due to risk of teratogenicity). There is an ongoing phase 1 study of HCV DAA treatment of pregnant women.[4] It is evaluating the pharmacokinetics and safety of the fixed dose combination of ledipasvir/sofosbuvir and is expected to be completed by September 2019. Women who are on antiviral treatment and become pregnant should discuss the potential risks and benefits of continuing therapy with their physicians. Pregnant women with cirrhosis should be counselled about the risks of adverse maternal and fetal outcomes and should be co-managed with a maternal-fetal medicine specialist.

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The risk of a pregnant woman transmitting HCV to her fetus or infant is 5.8% and with human immunodeficiency virus (HIV) co-infection, that risk almost doubles to 10.8%.[5] Transmission may occur during pregnancy, as a result of transplacental passage of the virus, or during vaginal or cesarean delivery. Vertical transmission is generally confined to women who have detectable HCV RNA during pregnancy, but has been reported in women with undetectable HCV RNA as viremia can be intermittent. There is an increased risk of HCV transmission with higher viral loads. When HCV is acquired during pregnancy, the risk of transmission is higher due to higher RNA levels. Obstetric procedures and prolonged rupture of membranes (PROM) are additional risk factors for transmission. Mother-to-child-transmission (MTCT) is not associated with HCV genotype, mode of delivery or breastfeeding. However, women should be advised to abstain from breastfeeding if their nipples are cracked or bleeding.

The main strategy for reducing the risk of vertical HCV transmission is to identify and treat HCV-infected women prior to conception (Figure 1). Unfortunately, risk-based screening probably misses many HCV infected patients, including pregnant women.[6] This was also the case in the early days of HBV screening, which is now universally recommended. Guidelines jointly published by the American Association for the Study of Liver Diseases and Infectious Diseases Society of American recommend screening for HCV infection during pregnancy.[7] There are many advantages to this approach. Knowledge of HCV status allows for education and appropriate referrals for the pregnant woman. Obstetricians would be able to avoid performing invasive procedures which pose a risk for transmission to the fetus. The infant will be identified as perinatally exposed to HCV so that testing can be performed at the appropriate time. Moreover, children previously born to an HCV-infected woman can be tested for HCV. Women can be counselled about the availability and benefits of antiviral treatment at the conclusion of the current pregnancy, with obvious health benefits to the mother, but also to prevent perinatal transmission during future pregnancies. Finally, women who are identified as infected could facilitate the evaluation and treatment of their sexual and IDU partners and thereby increase the public health benefit of screening. A recent study concluded that universal screening for HCV, including for pregnant women and women of childbearing age, would be cost effective.[8]

Figure 1. Algorithm for diagnostic testing for HCV.

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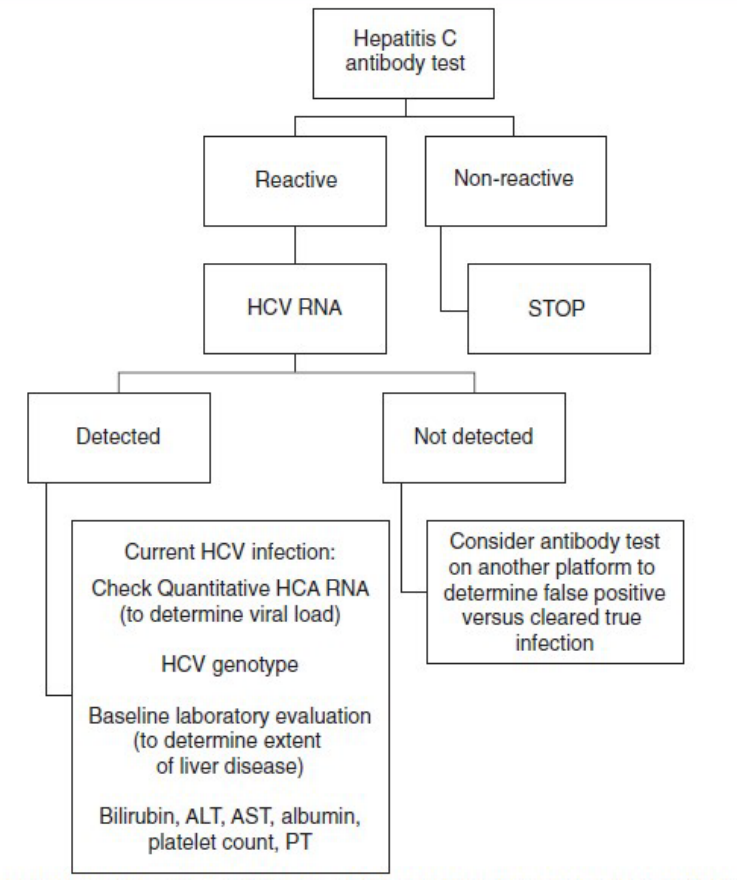

Differing from the above, the American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine recommend targeted HCV screening during pregnancy with a focus on high risk groups including women who have used illicit drugs, women on long-term hemodialysis, women with percutaneous/parenteral exposures in an unregulated setting (e.g. unlicensed tattoo parlors), recipients of transfusion or organ transplantations before 1992, recipients of blood products from a donor who later tested positive for HCV, women with a history of incarceration, women being evaluated for sexually transmitted infections (STIs), and those with chronic liver disease.[9] ACOG recommends testing high risk women for HCV at their first prenatal visit and later in pregnancy if there are new or persistent risk factors. Other recommendations include that HCV-infected women be screened for other STIs and should also be counselled to refrain from alcohol use. ACOG further recommends that women undergoing invasive prenatal diagnostic testing (e.g. amniocentesis) be counselled that data on vertical transmission, while limited, are reassuring. Obstetrical providers should avoid internal fetal monitoring and episiotomy, as well as PROM. Cesarean delivery has not been shown to reduce vertical transmission and ACOG recommends against this solely for the indication of HCV infection. Finally, providers should not discourage breastfeeding because of maternal HCV infection.

There is growing enthusiasm and support for universal screening. Kentucky, a state with a high incidence of HCV in the general population, has enacted legislation mandating HCV screening of all pregnant women.

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Infants who acquire HCV perinatally are completely asymptomatic. Their liver function tests are usually normal and 20% spontaneously clear their HCV, like the adult population. The 80% who are chronically infected will eventually develop liver disease, usually taking years to decades, with the concomitant risk of hepatocellular carcinoma. Co-morbidities like HIV or HBV co-infection, alcohol dependence, and obesity can hasten the progression of liver disease.

Unfortunately, multiple studies demonstrate low rates of testing of perinatally HCV-exposed infants. In Philadelphia, only 16% of infants with perinatal HCV exposure underwent HCV testing.[10] A report from Pittsburgh indicated that 30% of infants with perinatal HCV exposure were ever tested for HCV.[11] A recently published study from Boston demonstrated the enormity of the problem in women with opioid use, but also presented more favorable data in terms of infant testing.[12] Of 744 women with opioid use disorder who were tested for HCV infection, 510 (69%) were seropositive. Of the 404 infants born to seropositive women, 273 (78%) were tested at least once for HCV and 12 were diagnosed with chronic HCV infection. In Delaware, there are no current data concerning follow up of HCV-exposed infants.

Pediatric follow up of these infants is of paramount importance. Frequently, pediatric providers will see these infants due to neonatal abstinence syndrome (NAS). Women who deliver babies with NAS, if not already tested, should have their HCV status assessed. Newborns can be tested for antibody to HCV as well, but providers should realize that transplacentally transferred maternal IgG will cause a positive result until 18 months of age.

Current recommendations for the diagnosis of HCV infection in childhood are:

- Anti-HCV antibody at $\geq$ 18 months of age is the gold standard.
- HCV RNA between 1 and 2 months of age can be used if the 18 month antibody testing cannot be assured.
- Infants with negative HCV RNA results should still have the 18 month antibody test if possible.[13]

Treatment recommendations for children are limited. Ledipasvir/sofosbuvir and ribavirin/sofosbuvir are recommended for certain adolescents with HCV, but there is no current treatment available for children under 12 years of age. Other pediatric recommendations for DAAs are expected soon.

Conclusion

Women of childbearing potential and women who are pregnant comprise a very important population of HCV-infected persons. Identification of these women is critical, in order to link them to care and provide appropriate evaluation and treatment. Opportunities exist to improve HCV screening rates of these women and to test their children. Antiviral treatment during pregnancy and in early childhood are areas in urgent need of research.

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