Hepatitis C and Pregnancy

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Epidemiology

In the USA, the highest incidence of HCV is in the 20–29-year-old age group, and while new cases are likely under-reported, more than 30,000 new cases were estimated for 2014 [1–3]. Fifteen to twenty-five percent of persons with an acute infection will clear the virus, while the remaining 75–85% develop chronic infection [3]. Approximately 2.7–3.9 million people in the USA are living with chronic HCV, with the highest prevalence in those with repeated or large percutaneous blood exposures (i.e., injection drug users) [3, 4].

Consequences of chronic HCV include chronic liver disease (60–70%), cirrhosis (5–20%), and death from associated complications (1–5%) [3]. In the USA, chronic HCV is the primary reason for liver transplantation [3]. According to the Centers for Disease Control and Prevention (CDC) surveillance for 2010–2014, US mortality rates secondary to HCV have increased from 4.7 deaths per 100,000 to 5 deaths per 100,000 [2]. Globally, in 2013 there were an estimated 704,000 deaths due to HCV and associated morbidities, increased from 333,000 in 1990; however, the incidence of HCV has decreased [1, 5, 6]. This discordance is due to the idle period between infection and complications such as cirrhosis and hepatocellular carcinoma (HCC) [4].

The true prevalence of HCV in pregnant women or women of childbearing age in the USA is not known due to challenges capturing high-risk groups. The National Health and Nutrition Examination Survey provides estimates on the prevalence of

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hepatitis in the USA, but the data do not include populations such as the homeless, prisoners, or institutionalized persons [7]. Based on the existing data, prevalence rates in women of childbearing age have been reported at 1–1.6% [7, 8]. Among women with HCV and the presence of HCV RNA, rates of vertical transmission range from approximately 3 to 7% (median, 5%) [4, 9–11]. Among HCV-positive women with undetectable HCV RNA, vertical transmission is rare [9, 11, 12]. HIV coinfection increases HCV transmission several folds, up to 15% [3, 12]. Clearance rates among vertically infected children have been reported to be approximately 20–40% [13].

Pathogenesis

Hepatitis C virus is an RNA virus from the Flaviviridae family. There are 6 genotypes and more than 90 subtypes, and knowledge of these genotypes guides the choice of antiviral therapy [4]. Approximately 74% of cases in the USA are caused by genotype 1 [4]. In the USA, HCV is most commonly transmitted through injection drug use, but prior to 1992 when routine screening was implemented, blood transfusion was a leading cause. With the implementation of screening of blood and blood products, the risk of HCV from a transfusion is now less than 1 in 2 million units [3]. Since the virus is transmitted through infected blood and blood products, risk factors for transmission also include chronic hemodialysis, having received donated organs or tissues before 1992, occupational exposure, sexual contact with an HCV-infected partner, and being born to an HCV-infected mother [1, 3, 4, 14]. In contrast to hepatitis B virus (HBV), sexual transmission and vertical transmission are less efficient means of transmission of HCV [3].

Risk factors for vertical transmission: High maternal viremia is associated with vertical transmission; however, a critical titer has not yet been defined. In a cohort study of 190 infants born to HCV RNA-positive and human immunodeficiency (HIV)-negative women, mean RNA levels in those who transmitted HCV versus those who did not transmit were 8.9×10^6 genome copies/mL and 2.2×10^6 genome copies/mL, respectively [15]. A systematic review of 77 studies reported increased vertical transmission at HCV RNA titers greater than 10^5 to 10^6 copies/mL [11].

Maternal coinfection with HIV increases the risk of vertical transmission of HCV. A recent meta-analysis of the risk of vertical transmission of HCV showed transmission rates of 5.8% in HIV-negative mothers, versus 10.8% in HIV-positive mothers [12]. This is thought to be secondary to higher HCV viral loads in HIV-positive women [12, 16]. Additionally, one study showed that infants who are infected with HIV are at a 3.2-fold greater risk of acquiring HCV from co-infected mothers [17].

A cohort study by Mast et al. [9] identified prolonged rupture of membranes (>6 h) and the use of internal fetal monitoring devices as risk factors for transmission of HCV. Infection of peripheral blood mononuclear cells (PBMCs) by HCV has also been shown to increase the risk of transmission. This may be due to the

PBMCs serving as an HCV vector or because HCV variants that are able to infect PBMCs can more easily pass the placental barrier [18].

Factors not found to be associated with an increased risk of transmission of HCV include amniocentesis, route of delivery, and breastfeeding [19–22]. While amniocentesis has not been shown to be associated with vertical transmission, the American College of Obstetricians and Gynecologists (ACOG) suggest that noninvasive prenatal screening options be discussed with these patients [20]. According to ACOG and the American Academy of Pediatrics, breastfeeding is not contraindicated in pregnancy, and although HCV RNA and antibody have been detected in breast milk, no cases of HCV transmission through breast milk have been reported [19, 20].

Box 1 Risk Factors for Vertical Transmission of Hepatitis C Virus

Maternal

- High HCV viral load
- HIV coinfection
- Injection drug use
- Peripheral blood mononuclear cell infection
- Prolonged rupture of membranes
- Internal fetal monitoring (i.e., fetal scalp electrode)

Neonatal

- HIV coinfection

Risks of hepatitis C in pregnancy: Several pregnancy complications are associated with HCV infection. A recent meta-analysis showed that the risk of intrahepatic cholestasis of pregnancy is higher in women infected with HCV than in those without HCV (OR 20.4, 95% CI, 9.39–44.33) [23]. There is also a significant association with HCV and intrauterine fetal growth restriction and low birth weight [24]. Additional studies report associations with HCV and gestational diabetes and preterm labor as well as congenital anomalies, need for assisted ventilation, and neonatal intensive care unit (NICU) admission for the infant [25–27].

Clinical Findings

Acute infection in adults: After an incubation period of approximately 4–12 weeks (range, 2–24 weeks), symptoms of HCV may present in 20–30% of infected individuals; however, most people with HCV are asymptomatic [3]. Common symptoms include fever, nausea, vomiting, abdominal pain, fatigue, jaundice, and loss of appetite [1, 3].

Acute infection in infants: Infected infants are usually asymptomatic at birth and during childhood [3].

Chronic infection: Chronic HCV progresses in a slow and subtle manner, often without any signs for two decades, until complications arise, usually from

developing hepatic fibrosis [4]. Some may also develop conditions such as glomerulonephritis, cryoglobulinemia, and porphyria cutanea tarda, likely due to the immunologic response to infection [3, 4, 14].

Diagnosis

The diagnosis of HCV in pregnancy begins with a thorough history and physical exam, including screening for risk factors, such as injection drug use, family history, and coinfection with HIV. Although routine screening for HCV in pregnancy is currently not recommended, the CDC and ACOG recommend screening for women with significant risk factors [3, 20]. Testing of pregnant women is recommended in the following cases:

- All persons born between 1945 and 1965
- History of injection drug use
- Recipients of clotting factor concentrates prior to 1987
- Recipients of donated blood or organs prior to 1992
- Persons with HIV infection
- Persons with evidence of liver disease
- Persons on chronic hemodialysis

Maternal (and children age > 18 months) testing for HCV infection starts with identification of antibodies to HCV (anti-HCV) with enzyme immunoassays; however, antibody may not yet be positive if exposure was in the past 6–10 weeks [20]. If the test is positive, it should be followed with quantitative HCV RNA reverse-transcriptase polymerase chain reaction (RT-PCR), to confirm ongoing infection [4, 14]. HCV RNA can be detected within 1–2 weeks of exposure, making it an option for follow-up of a negative anti-HCV serologic test after a recent exposure to HCV [4, 28]. Table 1 provides an interpretation of the tests.

Table 1 Interpretation of hepatitis C serologic markers

Serologic test	Result	Interpretation
HCV antibody	Nonreactive	No HCV antibody, no further testing[a]
HCV antibody	Reactive	Past or current infection[b]
HCV antibody HCV RNA	Reactive Detected	Current HCV infection
HCV antibody HCV RNA	Reactive Not detected	No current infection[c]

Adapted from [28]

[a]If there has been a recent exposure to HCV, consider HCV RNA testing or follow-up antibody testing

[b]The possibility of a false-positive antibody test exists

[c]If there is a need to differentiate between a true- versus false-positive antibody test, another antibody assay (i.e. RIBA) can be done

Once a diagnosis of HCV is made, additional laboratory studies should include testing for genotype to guide treatment when appropriate, liver function testing (e.g., alanine aminotransferase and coagulation studies including fibrinogen), and a complete blood count. All pregnant women should be tested for HBV and HIV as part of routine prenatal screening. All susceptible HCV-positive patients should be vaccinated against hepatitis A and B [14]. Injection drug users should be screened for tuberculosis [29]. Imaging studies, such as ultrasound, should also be completed to evaluate for liver fibrosis [14]. These individuals ultimately should be referred to a practitioner experienced in the management of chronic liver disease [14, 20].

Treatment

Pregnant women with acute HCV can often be managed in the outpatient setting, with inpatient treatment reserved for those with severe illnesses such as encephalopathy or coagulopathy [20]. Treatment of chronic HCV in pregnancy is not available, as none of the available antiviral therapies have been tested on pregnant women [29]. A commonly used antiviral medication, ribavirin, is teratogenic and has been shown to cause termination of pregnancy. It is contraindicated in pregnancy, and women who have used ribavirin should avoid becoming pregnant for 6 months after cessation of use [14, 29]. With the advent of new antiviral regimens that do not include ribavirin or pegylated interferon, treatment during pregnancy may be possible in the near future. If HCV is diagnosed before pregnancy, therapy should be initiated in combination with effective contraception, in order to optimally treat the infection and decrease the risk of vertical transmission in a future pregnancy [29].

Prevention

No immunoprophylaxis exists to prevent the transmission of HCV. Intrapartum considerations include limited use of internal monitoring devices, and if possible, avoidance of prolonged rupture of membranes, as these may increase the risk of transmission [15]. Infected mothers should be educated on methods to reduce the risk of transmission to household contacts. Breast milk is not a mode of transmission, and women should be encouraged to breastfeed unless they develop cracked or bleeding nipples, which may allow blood-borne transmission to the infant [19].

Infants born to HCV-positive mothers must be followed closely to evaluate for possible infection (Fig. 1). Anti-HCV testing should not be done sooner than 18 months of age, due to the possible persistence of maternal antibodies [3, 16]. However, studies suggest that antibody-based testing results in the detection of significantly less HCV-infected children than would be expected. For example,

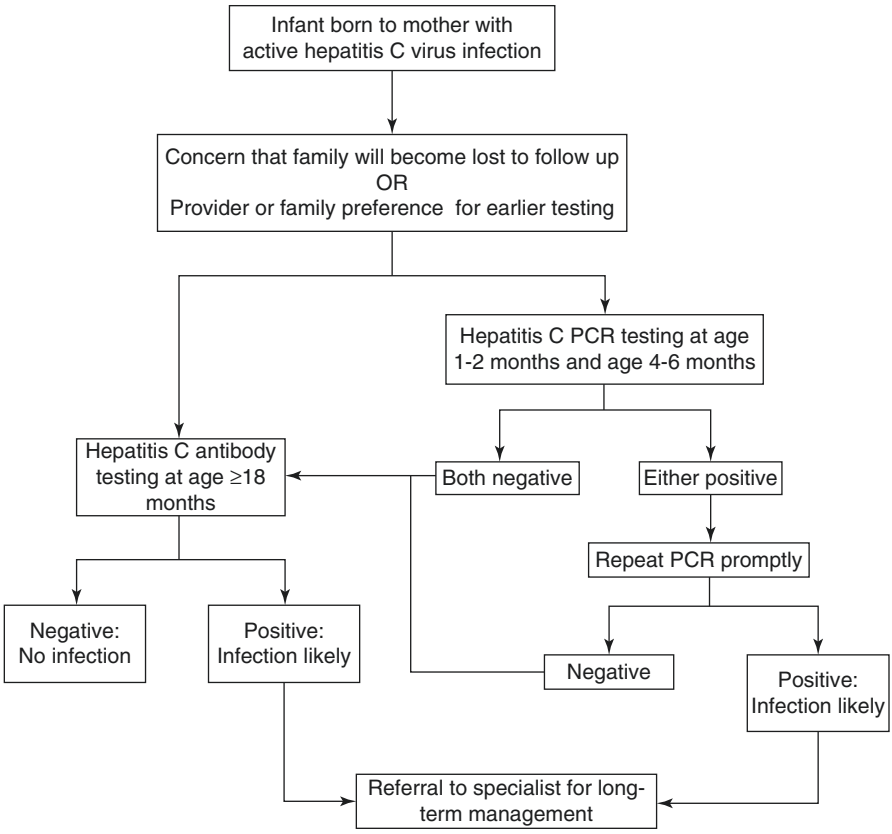

Fig. 1 Follow-up testing of infants born to mothers with active hepatitis C virus infection. *PCR* polymerase chain reaction

using Philadelphia public health registries, Kuncio et al. [30] identified only 4 HCV infections among 537 HCV-exposed infants, markedly less than the 27 (range, 15–38) infected infants that would be expected based on a mother-to-child transmission rate of 5% (range, 3–7%). As a result, some centers are increasingly moving to a PCR-based approach similar to the follow-up of HIV-exposed infants (see chapter "Management of HIV-Exposed Infants"). If PCR testing is performed, it should be done at age 1–2 months and again at age 4–6 months. Positive tests should be repeated at the next visit before confirming infection [4, 16]. Infants with negative PCR testing should still have confirmatory antibody testing after age 18 months.

Infected infants should be referred to a specialist in pediatric liver disease for long-term monitoring and consideration of antiviral therapy. Approximately 20–40% of infants will resolve acute HCV infection without progressing to chronic infection [13].

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