

# Hepatitis C in pregnancy: screening, treatment, and management

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The American College of Obstetricians and Gynecologists (ACOG) endorses this document.

In the United States, 1-2.5% of pregnant women are infected with hepatitis C virus, which carries an approximately 5% risk of transmission from mother to infant. Hepatitis C virus can be transmitted to the infant in utero or during the peripartum period, and infection during pregnancy is associated with increased risk of adverse fetal outcomes, including fetal growth restriction and low birthweight. The purpose of this document is to discuss the current evidence regarding hepatitis C virus in pregnancy and to provide recommendations on screening, treatment, and management of this disease during pregnancy. The following are Society for Maternal-Fetal Medicine recommendations: (1) We recommend that obstetric care providers screen women who are at increased risk for hepatitis C infection by testing for anti-hepatitis C virus antibodies at their first prenatal visit. If initial results are negative, hepatitis C screening should be repeated later in pregnancy in women with persistent or new risk factors for hepatitis C infection (eg, new or ongoing use of injected or intranasal illicit drugs) (GRADE 1B). (2) We recommend that obstetric care providers screen hepatitis C virus–positive pregnant women for other sexually transmitted diseases, including HIV, syphilis, gonorrhea, chlamydia, and hepatitis B virus (GRADE 1B). (3) We suggest that patients with hepatitis C virus, including pregnant women, be counseled to abstain from alcohol (Best Practice). (4) We recommend that direct-acting antiviral regimens only be used in the setting of a clinical trial or that antiviral treatment be deferred to the postpartum period as direct-acting antiviral regimens are not currently approved for use in pregnancy (GRADE 1C). (5) We suggest that if invasive prenatal diagnostic testing is requested, women be counseled that data on the risk of vertical transmission are reassuring but limited; amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter (GRADE 2C). (6) We recommend against cesarean delivery solely for the indication of hepatitis C virus (GRADE 1B). (7) We recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy in managing labor in hepatitis C virus–positive women (GRADE 1B). (8) We recommend that providers not discourage breast-feeding based on a positive hepatitis C virus infection status (GRADE 1A).

**Key words:** antiviral therapy, HCV, Hepatitis C virus, vertical transmission

## Introduction

Worldwide, up to 8% of pregnant women are infected with hepatitis C virus (HCV).<sup>1</sup> In the United States, the estimated prevalence of antenatal HCV infection is 1-2.5%; some studies estimate the prevalence to be as high as 4%.<sup>2</sup> The primary mode of HCV transmission is percutaneous exposure to blood from injection of illicit drugs. Other modes of transmission include vertical transmission (mother to child), sharing of contaminated devices for noninjection drug use,

exposure to infected blood through occupational and other means, and, although inefficient, sexual intercourse.<sup>3</sup>

Two primary concerns arise from HCV in pregnancy: (1) maternal well-being, ie, the effect of pregnancy on the course of chronic HCV infection; and (2) fetal well-being, namely mother-to-infant transmission of HCV and the impact of maternal infection on pregnancy outcomes.

## Epidemiology

### What is the natural course of HCV infection?

HCV can cause both acute and chronic hepatitis. The first 6 months after exposure to HCV is referred to as acute HCV infection. Acute HCV infection is asymptomatic in 75% of cases; when symptoms occur, they include abdominal pain, nausea, anorexia, jaundice, or malaise.<sup>4</sup> Without treatment,

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approximately 15% of infected individuals spontaneously clear HCV within 6 months of infection, although some estimate this number to be as high as 45%.<sup>5</sup> Those who do not clear the virus harbor it for the rest of their lives and develop chronic HCV infection; chronic infection accounts for most HCV-associated morbidity and mortality. As with the acute stage of infection, chronic HCV infection is usually asymptomatic, although it can cause progressive liver damage with serious consequences. Without treatment, 15-30% of patients with chronic HCV infection develop cirrhosis within 20 years<sup>5</sup>; 27% of those with cirrhosis develop hepatocellular carcinoma (HCC) within 10 years.<sup>6</sup> In comparison, among patients with cirrhosis who are treated with antiviral medications and achieve a sustained virological response (SVR), only 5% develop HCC within 10 years. HCC is a primary cause of mortality from HCV infection,<sup>7</sup> with a median length of survival after diagnosis of 20 months.<sup>8</sup>

### What is the impact of pregnancy on chronic hepatitis C?

Serum levels of alanine aminotransferase (ALT) tend to decrease during the second and third trimesters in pregnancies complicated by HCV infection and then return to prepregnancy levels after delivery.<sup>9-12</sup> In contrast, serum levels of HCV RNA may increase in infected women during the second and third trimesters of pregnancy. One study showed a statistically significant increase in HCV RNA,<sup>10</sup> whereas in another study, this trend was not statistically significant.<sup>12</sup> Researchers speculate that the increase in HCV RNA levels during pregnancy is due to down-regulation of the maternal immune response. Because hepatocellular damage caused by chronic HCV infection is thought to be immune-mediated rather than directly caused by viral cytotoxicity, down-regulation of the maternal immune response in pregnancy would be predicted to reduce the amount of hepatocellular damage caused by HCV, which would also account for the decrease in ALT levels.<sup>10</sup>

Histological evidence also suggests that pregnancy may be associated with a decrease in HCV-mediated hepatic injury. Resti et al<sup>13</sup> showed a beneficial effect of pregnancy on the progression of fibrosis, as determined by liver biopsy, in a retrospective cohort study of 157 pregnant women with chronic HCV infection. Specifically, they found that a history of pregnancy was independently associated with a lower likelihood of fibrosis progression.<sup>13</sup> In contrast, a small case-control study by Fontaine et al<sup>14</sup> showed worsening of histopathological measures after pregnancy. They compared liver biopsy samples from 12 HCV-positive women obtained before and after delivery, with samples from 12 nonpregnant HCV-positive women as controls. The mean period between initial and final biopsies was 4 years; during this time, 83% of pregnant patients showed deterioration in their necroinflammatory score, and 42% showed deterioration in their fibrosis score. In comparison, the rates

for controls were 25% and 8%, respectively.<sup>14</sup> These conflicting data highlight a need for additional study of the progression of fibrosis during pregnancy.

### What is the impact of HCV on pregnancy outcomes?

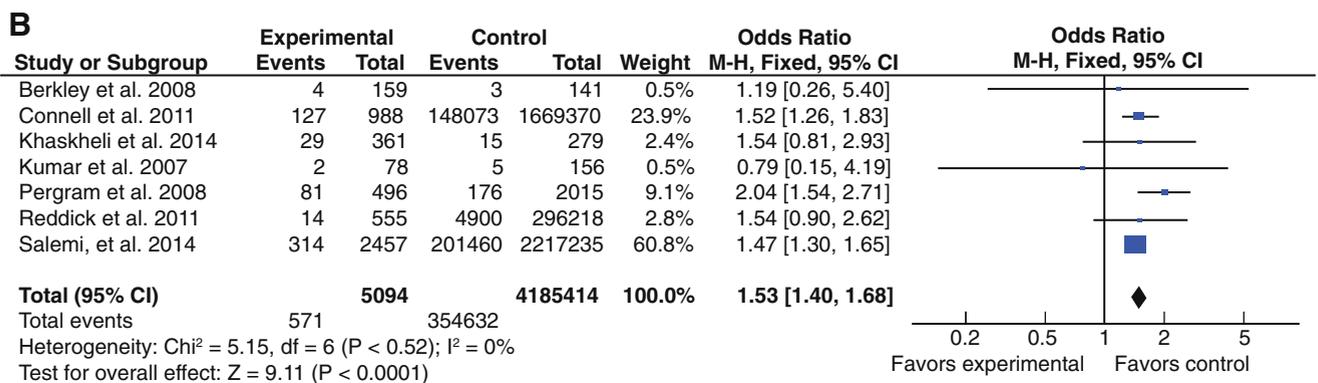
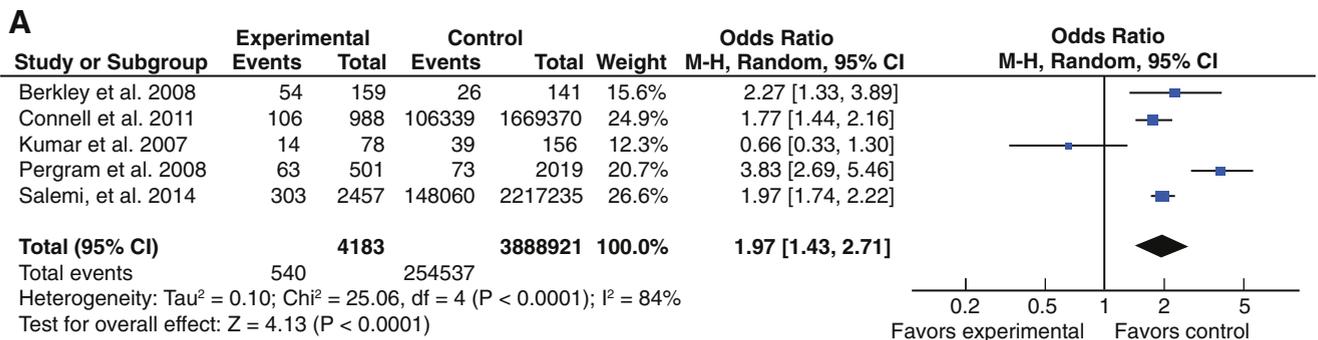
HCV infection is associated with adverse pregnancy outcomes. A population-based, retrospective cohort study from Washington state by Pergam et al<sup>15</sup> compared 506 HCV-positive pregnant women with 2022 HCV-negative pregnant controls. In multivariable analysis, it was found that infants born to women infected with HCV were more likely to be small for gestational age, have low birthweight, require admission to the neonatal intensive care unit, and require assisted ventilation.<sup>15</sup> Another population-based retrospective cohort study based in Florida by Connell et al<sup>16</sup> compared 988 HCV-positive women with 1,669,370 controls. Using multivariate analysis, it was found that HCV-infected women were more likely to deliver infants with poor birth outcomes, including preterm birth, low birthweight, and congenital anomalies. A recent meta-analysis that included these 2 studies and 5 others reported that maternal HCV infection was significantly associated with fetal growth restriction (odds ratio, 1.53; 95% confidence interval, 1.40–1.68) and low birthweight (odds ratio, 1.97; 95% confidence interval, 1.43–2.71) (Figure 1).<sup>17</sup> It is difficult to know with certainty whether the increased risk of such adverse fetal outcomes is due to the viral effect of HCV or to potential confounders in the population being studied.

The above-mentioned studies by Pergam et al<sup>15</sup> and Connell et al,<sup>16</sup> along with a population-based cohort study using the National Inpatient Sample, also reported higher rates of gestational diabetes in HCV-infected women compared with noninfected women.<sup>18</sup> However, in the Pergam et al<sup>15</sup> study, this association was limited to women with excessive weight gain during pregnancy. In another population-based, retrospective cohort study, Salemi et al<sup>19</sup> found that infants born to HCV-infected women were more likely to have feeding difficulties and other adverse neonatal outcomes, including cephalohematoma, brachial plexus injury, fetal distress, intraventricular hemorrhage, or neonatal seizures.

Intrahepatic cholestasis of pregnancy (ICP) has also been associated with HCV infection. Pregnant women with HCV have a significantly higher incidence of this disease—the overall incidence of ICP in the general obstetric population is 0.2-2.5%, while the odds of developing ICP are 20-fold higher in HCV-infected pregnant women.<sup>20</sup> Given the increased risk of fetal death associated with ICP, diagnosis of this disease in pregnant women is important.

Currently, a multicenter, prospective observational cohort study is underway to evaluate pregnancy outcomes of women with HCV; it is anticipated that this study will answer many of the unresolved questions regarding HCV in pregnancy. Outcomes being studied include preterm

**FIGURE 1**  
**Meta-analysis of infants of Hepatitis C virus-positive women**



Odds of **A**, low birthweight and **B**, fetal growth restriction in infants of hepatitis C virus-positive women: results of meta-analysis. Reprinted with permission.<sup>17</sup>

CI, confidence interval; df, days of freedom; M-H, Mantel-Haenszel.

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delivery, gestational diabetes, preeclampsia, cholestasis, and infant birthweight (Clinicaltrials.gov: NCT01959321).<sup>21</sup>

### What is the rate of vertical transmission of HCV?

Vertical transmission refers to viral transmission from mother to infant during pregnancy, delivery, or the neonatal period. At present, vertical transmission of HCV is the leading cause of HCV infection in children.<sup>22</sup> While one third to one half of mother-to-child transmission of HCV appears to occur in utero prior to the last month of pregnancy, the remainder is thought to occur either in the last month of pregnancy or during delivery.<sup>23</sup> In 2014, Benova et al<sup>24</sup> published a meta-analysis examining rates of vertical transmission of HCV, stratified by whether women were coinfecting with HIV. Pooling the results of 17 studies of women with chronic HCV infection who were HIV-negative, the risk of vertical transmission was 5.8%. In contrast, the risk of vertical transmission in HIV-positive women, based on the results of 8 studies, was almost doubled, at 10.8% (Figure 2).<sup>24</sup> The increased risk of vertical transmission in HIV-positive pregnant women may be due to increased HCV viral load resulting from HIV-mediated

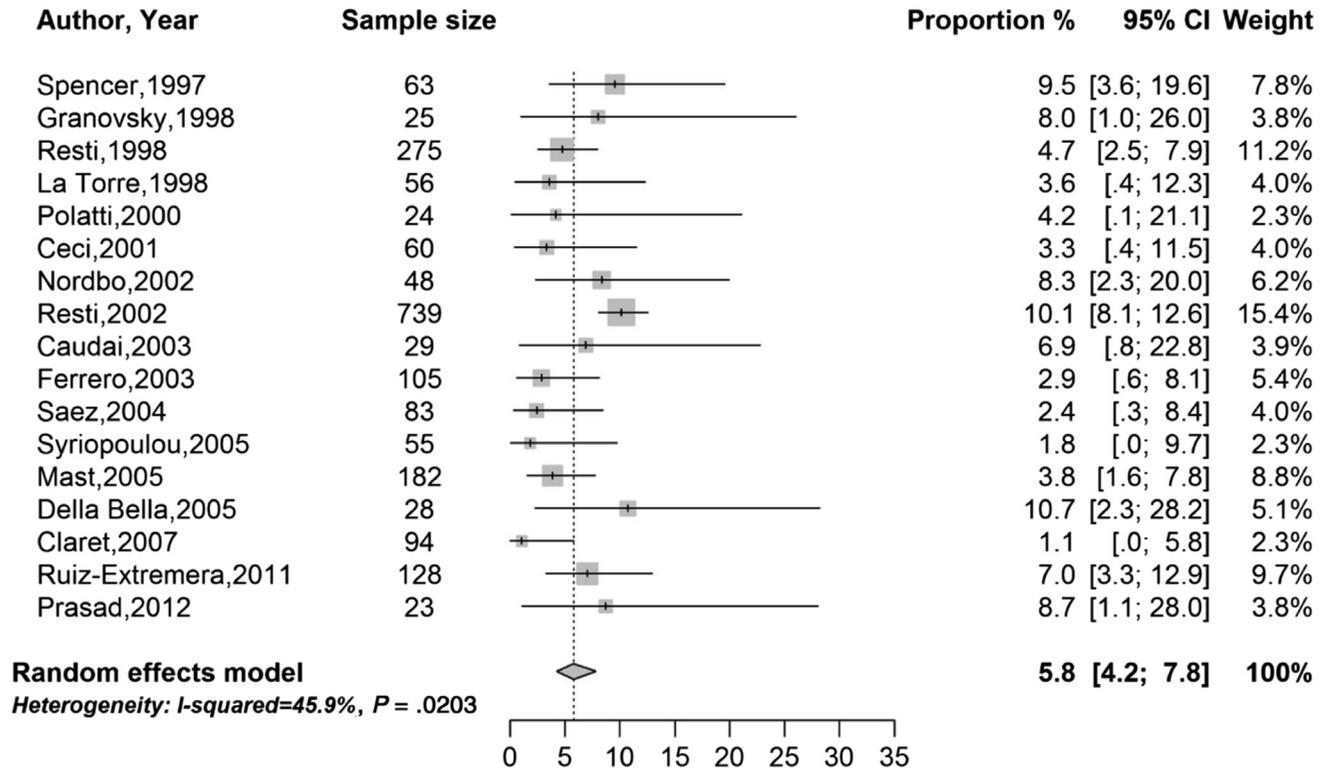
immunosuppression.<sup>24</sup> However, now that the use of highly active antiretroviral therapy in pregnant women with HIV is common in developed countries, the risk of vertical transmission of HCV in coinfecting women appears to be lower (4-8.5%).<sup>25,26</sup>

In general, vertical transmission of HCV is thought to be a risk only for women with detectable HCV RNA during pregnancy. The meta-analysis by Benova et al<sup>24</sup> included 15 studies with a total of 473 children born to women who were HCV-antibody-positive but RNA-negative. Only 1 of the 473 children was diagnosed with vertically acquired HCV infection.<sup>24</sup> Although there are other reports of vertical transmission from HCV RNA-negative women,<sup>27</sup> these cases may either be the result of insensitive methods for detecting HCV RNA or of intermittent HCV RNA positivity in these women.<sup>28</sup> In addition, whether the level of HCV viremia correlates with the risk of transmission has yet to be determined. Several studies have shown that higher viral loads correlate with an increased risk of transmission,<sup>28-30</sup> whereas other studies have failed to find this association.<sup>9,13</sup> Importantly, these studies involved a small number of vertically infected infants, ranging from 3-13.

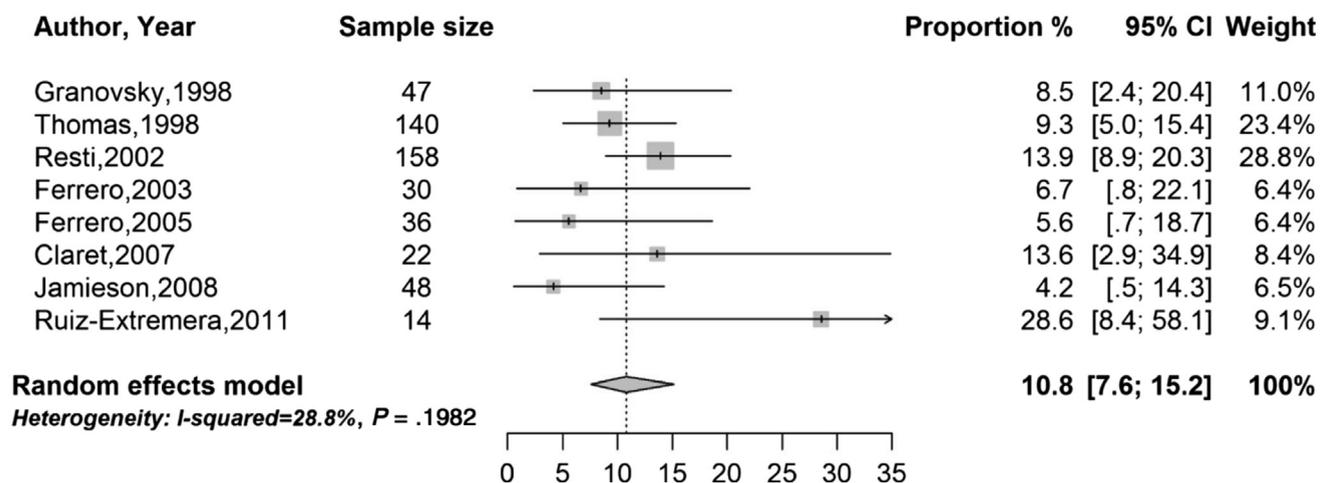
FIGURE 2

## Risk of hepatitis C virus vertical transmission: meta-analysis

## HIV-negative women



## HIV-positive women



Risk of hepatitis C virus (HCV) vertical transmission in infants  $\geq 18$  months of age born to anti-HCV-positive, HCV RNA-positive women by maternal HIV serostatus: results of meta-analysis. Reprinted with permission.<sup>24</sup>

CI, confidence interval.

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## Screening

### Who should be screened for HCV during pregnancy?

Current guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control and Prevention (CDC) recommend risk-based screening for HCV in pregnant women.<sup>4,31</sup> **We recommend that obstetric care providers screen women who are at increased risk for HCV by testing for anti-HCV antibodies at their first prenatal visit. If initial results are negative, HCV screening should be repeated later in pregnancy in women with persistent or new risk factors for HCV infection (eg, new or ongoing use of injected or intranasal illicit drugs) (GRADE 1B) (Table 1).** These criteria are based on guidelines from ACOG and from a joint commission of the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA).<sup>3,4</sup>

With the advent of direct-acting antiviral (DAA) therapy (discussed later) and the potential for treatment of HCV in pregnancy in the future, some researchers have proposed universal prenatal screening.<sup>32,33</sup> Another proposed benefit of universal screening would be the identification of more children who are at risk for HCV infection; risk-based screening fails to identify many HCV-positive women and therefore their newborns who are at risk.<sup>32</sup> However, without data that universal screening is cost-effective and without currently approved treatments for HCV in pregnancy, we concur with ACOG and the CDC in recommending against universal screening during pregnancy at this time.<sup>34</sup>

**TABLE 1**

#### Women in whom prenatal screening for hepatitis C virus is recommended<sup>3,4</sup>

Women who ever injected illegal drugs (even once)
Users of intranasal illicit drugs
Women ever on long-term hemodialysis
Women with percutaneous/parenteral exposures in unregulated setting (eg, tattoos received outside of licensed parlors or medical procedures done in settings without strict infection control policies)
Recipients of transfusions or organ transplants before July 1992 and recipients of clotting factor concentrates produced before 1987
Recipients of blood products from donor who later tested positive for HCV
Women with history of incarceration
Women seeking evaluation or care for sexually transmitted infection, including HIV
Women with unexplained chronic liver disease (including persistently elevated ALT)

ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus. Society for Maternal-Fetal Medicine. HCV in pregnancy. *Am J Obstet Gynecol* 2017.

### What is the ideal screening test for HCV?

Diagnosis of HCV infection depends on detection of anti-HCV antibodies and HCV RNA. Anti-HCV antibodies usually develop 2-6 months after exposure—during the acute phase of infection—and persist throughout life.<sup>35</sup> HCV viremia, ie, the presence of HCV RNA in the blood, indicates active infection and can first be detected 1-3 weeks after exposure.<sup>31</sup>

The standard screening test for HCV is an anti-HCV antibody test. A positive test result indicates one of the following: the patient has active HCV infection (acute or chronic), the patient had a past infection that has resolved, or the result is a false positive.<sup>3</sup> A positive anti-HCV antibody result should be followed by a quantitative nucleic acid test for HCV RNA. The recombinant immunoblot assay is no longer available or recommended (Figure 3). If a patient who tested negative for HCV RNA within the past 6 months is newly found to be viremic, acute HCV infection is confirmed. If a patient with no previous testing for hepatitis C tests positive for both anti-HCV antibodies and HCV RNA, it is not possible based on the test results alone to distinguish acute from chronic HCV infection. If the anti-HCV antibody test result is positive and the HCV RNA test result is negative, distinguishing a false-positive antibody test from a true infection requires testing for anti-HCV antibody with a different antibody assay platform, which should be performed according to CDC recommendations.<sup>36</sup> Finally, if a woman who may have been exposed to HCV within the last 6 months tests negative for anti-HCV antibodies, HCV RNA testing should be performed because the patient may not yet have seroconverted.<sup>3</sup>

## Treatment and outcomes

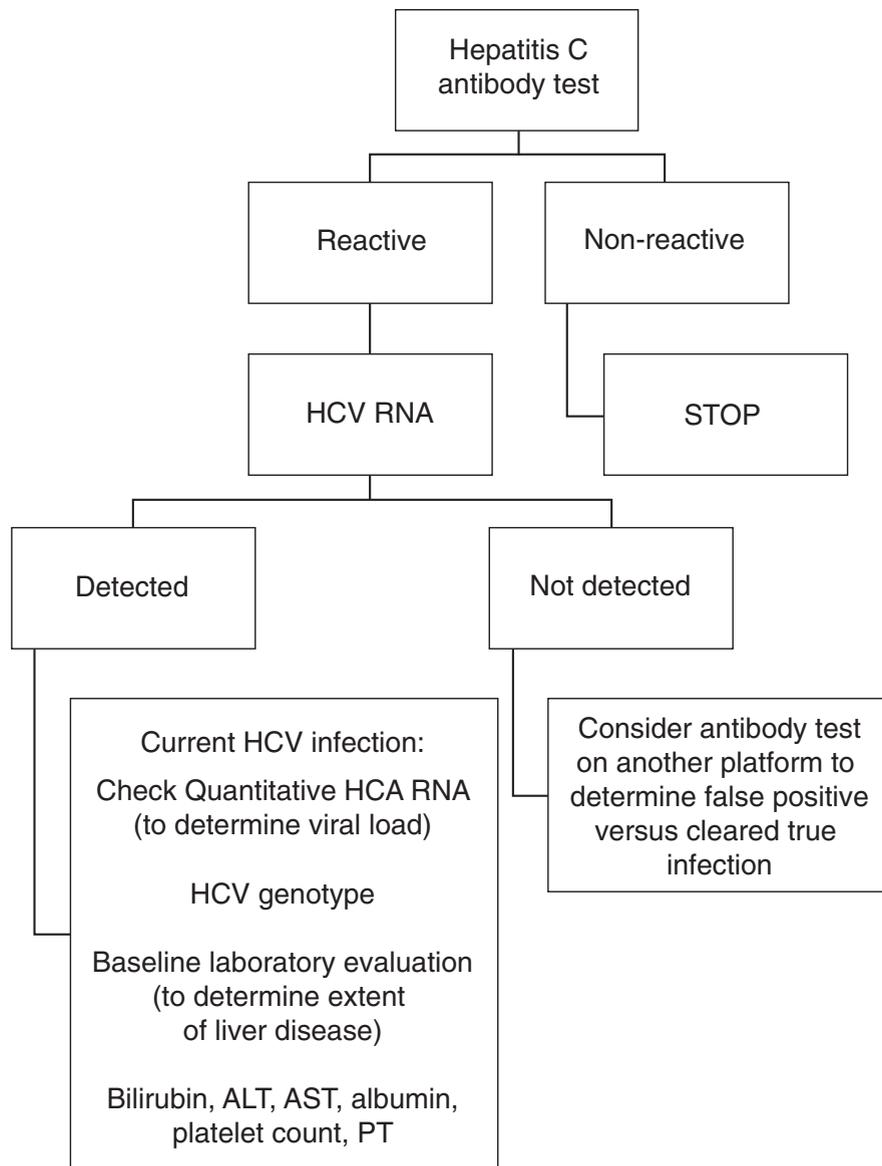
### Once hepatitis C is diagnosed, what additional evaluation should occur?

Because there are no formalized pregnancy-specific guidelines for laboratory testing in HCV infection, we have adapted guidelines from the AASLD/IDSA to pregnancy.<sup>3</sup> For pregnant women with confirmed active HCV infection, a quantitative HCV RNA test should be done to determine the baseline viral load. Basic laboratory testing to evaluate the extent of liver disease should include the following laboratory tests: bilirubin, ALT, and aspartate aminotransferase, albumin, platelet count, and prothrombin time. To help plan future treatment, testing for HCV genotype should also be performed (if not done previously).

In light of common risk factors, **we recommend that obstetric care providers screen HCV-positive pregnant women for other sexually transmitted diseases, including HIV, syphilis, gonorrhea, chlamydia, and hepatitis B virus (HBV) (GRADE 1B).** Hepatitis B has overlapping risk factors for HCV and can lead to accelerated liver damage and adverse effects during pregnancy. Patients with HBV infection and a high viral load can be offered antenatal treatment; infants should receive the hepatitis B vaccine as well as hepatitis immune globulin.<sup>37</sup>

FIGURE 3

## Recommended testing sequence for identifying current hepatitis C virus infection



Recommended testing sequence for identifying current hepatitis C virus (HCV) infection. Modified from Centers for Disease Control and Prevention. Available at: <https://www.cdc.gov/mmwr/pdf/wk/mm62e0507a2.pdf>.<sup>36</sup>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time.

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Hepatitis A infection can also worsen hepatic damage if present with HCV infection. The Advisory Committee on Immunization Practices recommends that women with HCV infection who are found to be at risk of HBV and/or hepatitis A virus be vaccinated against both of these agents,<sup>38</sup> and it is safe to do so during pregnancy.

### What are the principles of medical management of HCV?

Any woman who receives a diagnosis of HCV infection during pregnancy should be referred to a hepatologist or

infectious disease specialist experienced in the management of hepatitis to establish long-term care.

HCV is a genetically diverse RNA virus: it has 6 different genotypes that affect the choice and efficacy of treatment regimens. The goal of treatment is to achieve SVR, defined as undetectable HCV RNA 12-24 weeks after completing treatment. Since 99% of patients who achieve SVR remain HCV RNA-negative during long-term follow-up, SVR is considered indicative of cure of HCV. In patients who do not have cirrhosis, SVR is associated with resolution of liver disease. In patients with cirrhosis, regression of hepatic

fibrosis may be seen, and the risk of complications, such as hepatic failure, HCC, and portal hypertension, while still possible, is lower than in untreated individuals.<sup>39</sup>

Use of even modest amounts of alcohol has been associated with progression of liver disease, and **we suggest that patients with HCV, including pregnant women, be counseled to abstain from alcohol<sup>40</sup> (Best Practice)**. For patients with HCV who have normal hepatic function, dose adjustments in most prescription and over-the-counter medications are not required. Patients do not need to avoid acetaminophen, a commonly used analgesic, although it is advisable to set a lower maximum daily dose of 2 g rather than 4 g, as recommended for the general population.<sup>41</sup> For patients with advanced liver disease, dosage adjustments may be required for some medications.

Serial laboratory surveillance of liver function or serial viral load assessment during pregnancy in HCV-positive women is generally not recommended. As discussed previously, serum levels of ALT tend to decrease during the second and third trimesters of pregnancy,<sup>9-12</sup> ie, liver function is expected to improve, not worsen, during pregnancy.

### How is HCV treated in nonpregnant patients?

Since the discovery of HCV in 1989, treatment of the disease has advanced significantly. The standard-of-care treatment for chronic HCV until 2011 was with pegylated interferon (PegIFN)- $\alpha$  and ribavirin. Ribavirin is a guanosine analog nucleotide inhibitor that interrupts RNA metabolism required for viral replication,<sup>1</sup> and PegIFN- $\alpha$  is a cytokine released in response to viral infections.<sup>1</sup> Studies have shown that the combination of PegIFN- $\alpha$  and ribavirin results in SVR in only 40-80% of patients, depending on the HCV RNA genotype.<sup>39</sup> Moreover, PegIFN- $\alpha$ /ribavirin has a significant side-effect profile, including risk of severe infection, hemolytic anemia, depression, and a flu-like syndrome.<sup>5</sup>

In 2011, DAA medications were released, revolutionizing the treatment of HCV. These drugs directly inhibit the replication cycle of HCV through 1 of 3 targets: NS3/4A protease, NS5A protein, and NS5B RNA-dependent polymerase.<sup>5</sup> These proteins are involved in HCV replication; therefore, inhibiting them inhibits replication of the virus. DAA therapy has fewer side effects than interferon-based regimens and has led to higher SVR rates. DAA medications must be used in combination with PegIFN- $\alpha$ /ribavirin or at least one other DAA medication to prevent viral resistance.<sup>42</sup> However, IFN-containing regimens are rarely used now given the availability of DAA regimens; therefore, treatment regimens usually involve multiple DAA medications. DAA regimens have yielded SVR rates as high as 60-100%, depending on the severity of liver disease, the DAA medications used, the HCV RNA genotype, and the presence of resistance-conferring mutations in the HCV genome.<sup>39</sup>

The original first-generation DAA medications included boceprevir and telaprevir. Due to associated adverse

events, these medications are no longer recommended for treatment of HCV.<sup>5</sup> From 2014 through January 2016, 10 second-generation DAA medications were approved in the United States for treatment of HCV: dasabuvir, sofosbuvir, paritaprevir, grazoprevir, simeprevir, daclatasvir, ledipasvir, elbasvir, ombitasvir, and velpatasvir.<sup>5</sup>

In summary, according to guidelines released in 2016 by AASLD/ISDA, interferon-based regimens are no longer recommended for treatment of hepatitis C. Currently recommended DAA regimens typically achieve SVR rates of >90%, are better tolerated than interferon-based regimens, and require a shorter duration of treatment.<sup>3</sup> Treatment is recommended for all patients with chronic HCV, except those with short life expectancies that cannot be extended by treating hepatitis C.<sup>3</sup> Unfortunately, DAA regimens are prohibitively expensive for many patients.

### Should HCV be treated pharmacologically during pregnancy?

None of the antiviral therapies recommended for HCV infection are currently approved for use in pregnant women. Ribavirin is contraindicated in pregnancy because of its association with embryocidal and/or teratogenic effects in all animal species studied. Malformations of the gastrointestinal tract, skull, palate, jaw, limbs, skeleton, and eye have been observed in animal models.<sup>43</sup> In addition, because ribavirin can persist in nonplasma compartments for up to 6 months, the US Food and Drug Administration (FDA) cautions that pregnancy should be avoided in women taking ribavirin as well as in female partners of male patients taking ribavirin until 6 months after completing therapy.<sup>43</sup> It is recommended that at least 2 forms of effective contraception be used during treatment (of either the male or female partner) and for 6 months afterwards to prevent pregnancy.<sup>3,43</sup>

Studies are limited on the effects of second-generation DAA therapy in pregnancy. There are no adequate human data regarding any of these antivirals, and safety data come entirely from animal reproduction studies. The FDA has not categorized most of these drugs in terms of pregnancy safety (Table 2), likely because many of them were introduced after the FDA began eliminating A-B-C-D-X pregnancy drug categories in 2014.<sup>44</sup> Although limited animal data are available, sofosbuvir and ombitasvir/paritaprevir/ritonavir have not been demonstrated to confer a risk to the fetus.<sup>45,46</sup> The following DAA therapies do not have assigned FDA pregnancy categories: velpatasvir, daclatasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, ledipasvir, and elbasvir/grazoprevir. Again, the limited animal data that exist have not shown a risk to the fetus.<sup>47-51</sup> Another DAA therapy without an assigned FDA pregnancy category is simeprevir, which has shown fetal toxicity in animal studies.<sup>52</sup>

Due to the lack of human studies, no DAA therapy has yet been approved to treat HCV infection in pregnancy.<sup>1</sup> Given the availability of ribavirin-free DAA regimens that

**TABLE 2**  
**Use of direct-acting antiviral formulations**

Drug formulation	Genotype efficacy <sup>a</sup>	Details of use <sup>a</sup>
Sofosbuvir	All	Must be used with ribavirin or another DAA medication
Ombitasvir/paritaprevir/ritonavir	1, 4	Must be used with ribavirin or dasabuvir
Daclatasvir	1, 2, 3	Must be used with sofosbuvir, with or without ribavirin
Ledipasvir	1, 4, 5, 6	Must be used with sofosbuvir, with or without ribavirin
Velpatasvir	All	Must be used with sofosbuvir
Ombitasvir/paritaprevir/ritonavir/dasabuvir	1	
Elbasvir/grazoprevir	1, 4	
Simeprevir	1	Must be used with sofosbuvir, with or without ribavirin

DAA, direct acting antiviral.

<sup>a</sup> Source: US National Library of Medicine DailyMed. Of note, no drugs are currently approved by US Food and Drug Administration for treatment of hepatitis C in pregnancy. *Society for Maternal-Fetal Medicine. HCV in pregnancy. Am J Obstet Gynecol 2017.*

demonstrated high efficacy in nonpregnant adults and no adverse fetal effects in animal studies, the assessment of these regimens for use in pregnancy should be actively researched. Currently, a phase I trial is underway to test the pharmacokinetics and safety of ledipasvir plus sofosbuvir for treatment of chronic HCV infection during pregnancy (Clinicaltrials.gov: NCT02683005). The projected completion date of this study is September 2018.<sup>53</sup> In the meantime, if a woman becomes pregnant while taking one of the DAA therapies, animal data do not suggest teratogenic risk, but women should be counseled that human data are lacking.<sup>1</sup> **We recommend that DAA regimens only be used in the setting of a clinical trial or that antiviral treatment be deferred to the postpartum period as DAA regimens are not currently approved for use in pregnancy (GRADE 1C).**

### Methods to reduce maternal-fetal transmission

#### Is invasive prenatal diagnostic testing safe in pregnant women with HCV?

Amniocentesis does not appear to increase the risk of vertical transmission, although this conclusion is based on limited data.<sup>54</sup> Moreover, these studies have not addressed the potential impact of viral load and have been limited by small sample sizes. No association between amniocentesis and vertical transmission was found in a case-control study of 51 infected children that evaluated risk factors for vertical transmission or in a case series of 22 HCV-positive women who underwent amniocentesis.<sup>54</sup> No studies have been published on the risk of vertical transmission of HCV with other invasive prenatal testing modalities, including chorionic villus sampling. **We suggest that if invasive prenatal diagnostic testing is requested, women be counseled that data on the risk of vertical transmission are reassuring but limited; amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter (GRADE 2C).**

#### Does mode of delivery affect the risk of vertical transmission?

Mode of delivery—vaginal vs cesarean—has not been shown to be a risk factor for vertical transmission of hepatitis C. Cottrell et al<sup>55</sup> published a systematic review in 2013 that included 14 studies (all observational) evaluating the association between mode of delivery and vertical transmission of HCV. Eleven studies compared the risk of transmission between vaginal and cesarean delivery without differentiating between elective and emergent cesarean deliveries; of these, 10 found no association between mode of delivery and transmission rate. Two good-quality studies specifically compared elective cesarean delivery before the onset of labor with vaginal or emergent (after onset of labor) cesarean delivery. There was no statistically significant difference in the risk of vertical transmission according to mode of delivery in either of these 2 studies.<sup>27,28</sup> Moreover, a 2011 meta-analysis of studies on HCV vertical transmission by mode of delivery found no significant difference. This meta-analysis did not distinguish between elective and emergent cesarean deliveries and included 8 studies, all of which were observational.<sup>56</sup> Because all published studies on mode of delivery and the risk of vertical transmission of HCV are observational, and most did not assess viral load at the time of delivery, these results should be interpreted cautiously.<sup>57</sup>

**We recommend against cesarean delivery solely for the indication of HCV (GRADE 1B).**

#### Does labor management affect the risk of vertical transmission?

Several factors in labor management may be associated with an increased risk of vertical transmission of HCV, namely prolonged rupture of membranes, internal fetal monitoring, and episiotomy. One study reported that membrane rupture for >6 hours was associated with increased risk of vertical transmission.<sup>28</sup> Another study

found that the median duration of membrane rupture was significantly longer among women who transmitted HCV to their infants than among those who did not (28 vs 16 hours).<sup>58</sup> Regarding invasive fetal monitoring, a retrospective study including 710 HCV-infected women<sup>59</sup> and a prospective study including 242 HCV-infected women<sup>28</sup> both reported that internal fetal monitoring was associated with increased risk of transmission compared with no internal monitoring. In contrast, a retrospective study with 724 women found no association.<sup>60</sup> One of these studies also found that episiotomy was significantly associated with

an increased risk of vertical transmission.<sup>59</sup> Based on the available evidence, **we recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy in managing labor in HCV-positive women (GRADE 1B)**, unless it is unavoidable in the course of management (ie, when unable to trace the fetal heart rate with Doppler and the alternative is proceeding with cesarean delivery). We also recommend that obstetric care providers avoid early amniotomy and episiotomy in managing labor in HCV-positive women. Expectant management of ruptured membranes should be avoided at term and patients with ruptured membranes at term should be actively managed in labor. There are inadequate data regarding the perinatal risk of hepatitis C transmission with expectant management in the setting of prolonged preterm rupture of membranes. Therefore, usual obstetric management should not be altered because of hepatitis C infection.

### Summary of recommendations

Recommendations	GRADE
1 We recommend that obstetric care providers screen women who are at increased risk for HCV by testing for anti-HCV antibodies at their first prenatal visit. If initial results are negative, HCV screening should be repeated later in pregnancy in women with persistent or new risk factors for HCV infection (eg, new or ongoing use of injected or intranasal illicit drugs).	1B Strong recommendation, moderate-quality evidence
2 We recommend that obstetric care providers screen HCV-positive pregnant women for other sexually transmitted diseases, including HIV, syphilis, gonorrhea, chlamydia, and HBV.	1B Strong recommendation, moderate-quality evidence
3 We suggest that patients with HCV, including pregnant women, be counseled to abstain from alcohol.	Best Practice
4 We recommend that DAA regimens only be used in the setting of a clinical trial or that antiviral treatment be deferred to the postpartum period as DAA regimens are not currently approved for use in pregnancy.	1C Strong recommendation, low-quality evidence
5 We suggest that if invasive prenatal diagnostic testing is requested, women be counseled that data on the risk of vertical transmission are reassuring but limited; amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter.	2C Weak recommendation, low-quality evidence
6 We recommend against cesarean delivery solely for the indication of HCV.	1B Strong recommendation, moderate-quality evidence
7 We recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy in managing labor in HCV-positive women.	1B Strong recommendation, moderate-quality evidence
8 We recommend that obstetric care providers not discourage breast-feeding based on a positive HCV infection status.	1A Strong recommendation, high-quality evidence

### Postnatal issues related to HCV

#### Is breast-feeding safe in HCV-positive mothers?

Breast-feeding does not appear to affect the risk of vertical transmission of HCV. The Cottrell et al<sup>55</sup> systematic review included 14 cohort studies examining breast-feeding and HCV transmission, and none found a significant association. Therefore, ACOG and the CDC state that breast-feeding is safe in women with HCV infection<sup>4,31</sup>; however, the CDC recommends that women abstain from breast-feeding if their nipples are bleeding or cracked.<sup>31</sup> **We recommend that obstetric care providers not discourage breast-feeding based on a positive HCV infection status (GRADE 1A).**

### Guidelines

**The content of this document reflects the national and international guidelines related to the management of hepatitis C virus infection in pregnancy.**

Organization	Title	Year of publication
AASLD-IDSA <sup>3</sup>	Recommendations for testing, managing, and treating hepatitis C	2016
World Health Organization <sup>5</sup>	Guidelines for the screening, care, and treatment of persons with chronic hepatitis C infection	2016
American Academy of Pediatrics <sup>61</sup>	Hepatitis C	2015
European Association for the Study of the Liver <sup>39</sup>	Recommendations on treatment of hepatitis C	2015
CDC <sup>36</sup>	Testing for HCV infection: an update of guidance for clinicians and laboratories	2013
ACOG <sup>4</sup>	Viral hepatitis in pregnancy. Practice bulletin No. 86	2007

If women have cracked and bleeding nipples, milk should be expressed and discarded.

### How should infants born to HCV-positive women be screened for HCV infection?

Because anti-HCV antibodies can be transmitted across the placenta from a pregnant woman to the fetus, the presence of anti-HCV antibodies in a neonate's serum soon after delivery is not diagnostic of neonatal infection. In a prospective study of vertical transmission of HCV that included 235 uninfected infants, anti-HCV antibodies were found in 96.8% of infants at birth, 15.3% at age 12 months, 1.6% at age 18 months, and 1.0% at age 24 months.<sup>28</sup> This study defined infants as HCV infected if they were positive for HCV RNA on at least 2 occasions at age  $\geq 1$  month or older or if they were anti-HCV positive at 24 months of age.<sup>28</sup> The American Academy of Pediatrics and CDC recommend screening of infants born to HCV-positive women for anti-HCV antibodies  $>18$  months of age or for HCV RNA on 2 occasions in infants  $>1$  month of age.<sup>61</sup> ■

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