Considerations on the mode of delivery for pregnant women with hepatitis C infection

While the mode of delivery’s effect on vertical transmission rates of HCV infection is debated, 2 select groups of patients with HCV infection may benefit from cesarean delivery. The authors offer pertinent study data that can help guide decision making.

Morgan Brazel, BA, and Patrick Duff, MD

CASE Pregnant woman with chronic opioid use and HIV, recently diagnosed with HCV
A 34-year-old primigravid woman at 35 weeks’ gestation has a history of chronic opioid use. She previously was diagnosed with human immunodeficiency virus (HIV) infection and has been treated with a 3-drug combination antiretroviral regimen. Her most recent HIV viral load was 750 copies/mL. Three weeks ago, she tested positive for hepatitis C virus (HCV) infection. Liver function tests showed mild elevations in transaminase levels. The viral genotype is 1, and the viral load is 2.6 million copies/mL.

How should this patient be delivered? Should she be encouraged to breastfeed her neonate?

The scope of HCV infection
Hepatitis C virus is a positive-sense, enveloped, single-stranded RNA virus that belongs to the Flaviviridae family. There are 7 confirmed major genotypes of HCV and 67 confirmed subtypes. HCV possesses several important virulence factors. First, the virus’s replication is prone to frequent mutations because its RNA polymerase lacks proofreading activity, resulting in significant genetic diversity. The great degree of heterogeneity among HCV leads to high antigenic variability, which is one of the main reasons there is not yet a vaccine for HCV. Additionally, HCV’s genomic plasticity plays a role in the emergence of drug-resistant variants.

Virus transmission. Worldwide, approximately 130 to 170 million people are infected with HCV. HCV infections are caused primarily by exposure to infected blood, through sharing needles for intravenous drug injection and through receiving a blood transfusion. Other routes of transmission include exposure through sexual contact, occupational injury, and perinatal acquisition.

The risk of acquiring HCV varies for each of these transmission mechanisms. Blood transfusion is no longer a common mechanism of transmission in places where blood donations are screened for HCV antibodies and viral RNA. Additionally, unintentional needle-stick injury is the only occupational risk factor associated with HCV infection, and health care workers do not have a greater prevalence of HCV than the general population. Moreover, sexual transmission is not a

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Risk factors for HCV transmission from mother to child include HIV co-infection, internal fetal monitoring, and longer duration of membrane rupture.14 The effect that mode of delivery has on vertical transmission rates, however, is still debated, and a Cochrane Review found that there were no randomized controlled trials assessing the effect of mode of delivery on mother-to-infant HCV transmission.15

Serology and genotyping used in diagnosis
The serological enzyme immunoassay is the first test used in screening for HCV infection. Currently, third- and fourth-generation enzyme immunoassays are used in the United States.16 However, even these newer serological assays cannot consistently and precisely distinguish between acute and chronic HCV infections.17 After the initial diagnosis is made with serology, it usually is confirmed by assays that detect the virus's genomic RNA in the patient's serum or plasma.

The patient’s HCV genotype should be identified so that the best treatment options can be determined. HCV genotyping can be accomplished using reverse transcription quantitative polymerase chain reaction (RT-qPCR) amplification. Three different RT-qPCR assessments usually are performed using different primers and probes specific to different genotypes of HCV. While direct sequencing of the HCV genome also can be performed, this method is usually not used clinically due to its technical complexity.16

### TABLE 1 World Health Organization treatment recommendations for chronic HCV infection in adults without cirrhosis18,19

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Duration of treatment</th>
<th>Rate of SVR</th>
<th>Total cost for a single course of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>300 mg/120 mg</td>
<td>8 weeks</td>
<td>&gt; 94% for all genotypes</td>
<td>$40,000</td>
</tr>
<tr>
<td>Sofosbuvir/daclatasvir</td>
<td>400 mg/60 mg</td>
<td>12 weeks</td>
<td>&gt; 92% for genotypes 1, 2, 3, and 4; 88% for genotype 5; 94% for genotype 6</td>
<td>$91,000</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>400 mg/100 mg</td>
<td>12 weeks</td>
<td>&gt; 96% for all genotypes except genotype 3; 89% for genotype 3</td>
<td>$60,000</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.
Modern treatments are effective

Introduced in 2011, direct-acting antiviral therapies are now the recommended treatment for HCV infection. These drugs inhibit the virus’s replication by targeting different proteins involved in the HCV replication cycle. They are remarkably successful and have achieved sustained virologic response (SVR) rates greater than 90%.¹¹ The World Health Organization recommends several pan-genotypic (that is, agents that work against all genotypes) direct-acting antiviral regimens for the treatment of chronic HCV infection in adults without cirrhosis (TABLE 1).¹⁸,¹⁹ CONTINUED ON PAGE 42
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Unfortunately, experience with these drugs in pregnant women is lacking. Many direct-acting antiviral agents have not been tested systematically in pregnant women, and, accordingly, most information about their effects in pregnant women comes from animal models.11

Perinatal transmission rates and effect of mode of delivery

We compiled data from 11 studies that reported the perinatal transmission rate of HCV associated with various modes of delivery. These studies were selected from a MEDLINE literature review from 1999 to 2019. The studies were screened by title and then by abstract. Inclusion was restricted to randomized controlled trials, cohort studies, and case-control studies written in English. Study quality was assessed as good, fair, or poor based on the study design, sample size, and analyses performed. The results from the total population of each study are reported in TABLE 2 (page 41).14,20-29

Three studies separated data based on the mother’s HIV status. The perinatal transmission rates of HCV for mothers co-infected with HIV are reported in TABLE 3.23,27 The results for HIV-negative mothers are reported in TABLE 4.14,23

Finally, 2 studies grouped mothers according to their HCV viral load. All of the

### TABLE 3 Effect of mode of delivery on perinatal transmission rates of HCV in mothers co-infected with HIV

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of study; quality of evidence</th>
<th>No. of patients delivered by cesarean</th>
<th>No. of patients delivered vaginally</th>
<th>Perinatal transmission rate (%) in all patients delivered by cesarean</th>
<th>Perinatal transmission rate (%) in patients who had vaginal delivery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Paediatric Hepatitis C Virus Network, 200123</td>
<td>Retrospective cohort; good</td>
<td>159</td>
<td>329</td>
<td>8.2</td>
<td>17.3</td>
<td>.008</td>
</tr>
<tr>
<td>Delotte, 201427</td>
<td>Cohort; good</td>
<td>38</td>
<td>17</td>
<td>10.5</td>
<td>11.8</td>
<td>.892a</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCV, hepatitis C virus; HIV, human immunodeficiency virus.

a P value not reported in original study.

### TABLE 4 Effect of mode of delivery on perinatal transmission rates of HCV in HIV-negative mothers

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of study; quality of evidence</th>
<th>No. of patients delivered by cesarean</th>
<th>No. of patients delivered vaginally</th>
<th>Perinatal transmission rate (%) in all patients delivered by cesarean</th>
<th>Perinatal transmission rate (%) in patients who had vaginal delivery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Paediatric Hepatitis C Virus Network, 200123</td>
<td>Retrospective cohort; good</td>
<td>218</td>
<td>666</td>
<td>6.9</td>
<td>5.9</td>
<td>.58</td>
</tr>
<tr>
<td>Mast, 200514</td>
<td>Cohort; good</td>
<td>30</td>
<td>151</td>
<td>3.3</td>
<td>4.0</td>
<td>.55</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCV, hepatitis C virus; HIV, human immunodeficiency virus.
mothers in these studies were anti-HCV antibody positive, and the perinatal transmission rates for the total study populations were reported previously in TABLE 2. The results for mothers who had detectable HCV RNA are reported in TABLE 5.20,21 High viral load was defined as ≥ 2.5 x 10^6 Eq/mL in the study by Okamoto, which is equivalent to ≥ 6.0 x 10^5 IU/mL in the study by Murakami.

For most, CD does not reduce HCV transmission
Nine of the 11 studies found that the mode of delivery did not have a statistically significant impact on the vertical transmission rate of HCV in the total study populations.14,22-29 The remaining 2 studies found that the perinatal transmission rate of HCV was lower with cesarean delivery (CD) than with vaginal delivery.20,21 When considered together, the results of these 11 studies indicate that CD does not provide a significant reduction in the HCV transmission rate in the general population.

Our review confirms the findings of others, including a systematic review by the US Preventive Services Task Force.30 That investigation also failed to demonstrate any measurable increase in risk of HCV transmission as a result of breastfeeding.

Cesarean delivery may benefit 2 groups.
Careful assessment of these studies, however, suggests that 2 select groups of patients with

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**TABLE 5** Effect of mode of delivery on perinatal transmission rates of HCV in mothers who had detectable HCV RNA

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of study; quality of evidence</th>
<th>No. of patients delivered by cesarean</th>
<th>No. of patients delivered vaginally</th>
<th>Perinatal transmission rate (%) in all patients delivered by cesarean</th>
<th>Perinatal transmission rate (%) in patients who had vaginal delivery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto, 200020,a</td>
<td>Prospective cohort; poor</td>
<td>18</td>
<td>41</td>
<td>0.0</td>
<td>17.1</td>
<td>.089</td>
</tr>
<tr>
<td>Murakami, 201221,a, b</td>
<td>Prospective cohort; fair</td>
<td>20</td>
<td>56</td>
<td>0.0</td>
<td>17.9</td>
<td>.055</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus.

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**TABLE 6** Effect of mode of delivery on perinatal transmission rates of HCV in mothers with high viral loads, defined as ≥ 2.5 x 10^6 Eq/mL in the study by Okamoto, which is equivalent to ≥ 6.0 x 10^5 IU/mL in the study by Murakami

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of study; quality of evidence</th>
<th>No. of patients delivered by cesarean</th>
<th>No. of patients delivered vaginally</th>
<th>Perinatal transmission rate (%) in all patients delivered by cesarean</th>
<th>Perinatal transmission rate (%) in patients who had vaginal delivery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto, 200020,a</td>
<td>Cohort; poor</td>
<td>10</td>
<td>16</td>
<td>0.0</td>
<td>43.8</td>
<td>.023</td>
</tr>
<tr>
<td>Murakami, 201221,a, b</td>
<td>Cohort; fair</td>
<td>9</td>
<td>22</td>
<td>0</td>
<td>40.9</td>
<td>.032</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus.

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HCV may benefit from CD:
- mothers co-infected with HIV, and
- mothers with high viral loads of HCV.

In both of these populations, the vertical transmission rate of HCV was significantly reduced with CD compared with vaginal delivery. Therefore, CD should be strongly considered in mothers with HCV who are co-infected with HIV and/or in mothers who have a high viral load of HCV.

CASE Our recommendation for mode of delivery
The patient in our case scenario has both HIV infection and a very high HCV viral load. We would therefore recommend a planned CD at 38 to 39 weeks’ gestation, prior to the onset of labor or membrane rupture. Although HCV infection is not a contraindication to breastfeeding, the mother’s HIV infection is a distinct contraindication.

References