HCV in Pregnancy: Test and Treat?

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Newly Reported Chronic Hepatitis C in the US, 2018

Number of newly reported* Hepatitis C cases by sex and age in the United States, 2018 (N=137,713)

* Data was not either not reportable by law statute or regulation, not reported or otherwise unavailable from Alabama, Arkansas, California, Delaware, District of Columbia, Hawaii, Indiana, Kentucky, Mississippi, Nevada, North Carolina Rhode Island, and Texas

[Graph showing number of newly reported Hepatitis C cases by sex and age in the United States, 2018 (N=137,713).]

### Maternal Characteristics

**Hepatitis C vs Non-Hepatitis C–Affected Pregnancies**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCV N=561,162 n (%)</th>
<th>Non-HCV N=515,203,728 n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>48,721 (79.7)</td>
<td>7,927,310 (52.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>2892 (4.7)</td>
<td>2,161,667 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Asian</td>
<td>770 (1.3)</td>
<td>958,060 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4976 (8.1)</td>
<td>3,556,295 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3803 (6.2)</td>
<td>590,396 (3.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Social Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>15,032 (24.7)</td>
<td>8,838,815 (60.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Less than 12th-grade education</td>
<td>15,654 (26.0)</td>
<td>2,130,022 (14.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid</td>
<td>47,320 (78.3)</td>
<td>6,484,281 (42.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prenatal Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>15,747 (25.8)</td>
<td>5,906,993 (38.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of prior cesarean birth</td>
<td>12,153 (19.9)</td>
<td>2,229,287 (15.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of preterm birth</td>
<td>5180 (8.5)</td>
<td>448,129 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>36,929 (61.4)</td>
<td>1,101,519 (7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No prenatal care</td>
<td>3412 (5.9)</td>
<td>228,556 (1.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hepatitis C infection is associated with increased risk of gestational diabetes, cholestasis of pregnancy, and preterm birth.

Universal HCV Screening Now Recommended UNIVERSALLY

2018

2019

2020

May 2021

June 2021
Reasons Cited for Universal Hepatitis C Screening

- Seeing increases in prevalence of Hepatitis C during pregnancy
- Risk-based screening misses many Hepatitis C cases
  - Providers don’t ask, patients don’t tell
  - Risks identified; Hepatitis C test still not ordered
- Pregnancy is a window of opportunity for Hepatitis C testing
- Easy to implement – already universal screening for HIV and Hepatitis B
- Identifying all Hepatitis C cases can improve outcomes
  - Mom: harm reduction counseling, linkage to Hepatitis C care/treatment
  - Baby: intrapartum transmission risk reduction, screening for perinatal transmission
- Universal screening in pregnancy is cost-effective

Jhaveri R, et al CID 2018
Chaillon A, et al CID 2019
Perinatal Hepatitis C Transmission

- What is the rate of perinatal Hepatitis C transmission?
  - 5.8% (95% CI 4.2-7.80) (HIV negative)\(^1\)
  - 10.8% (95% CI 7.6-15.2) (HIV co-infected)\(^1\)

- Risk factors for perinatal Hepatitis C transmission
  - Prolonged rupture of membranes\(^2\)
  - Obstetric procedures and intrapartum events that lead to infant exposure to Hepatitis C-infected maternal blood; eg, internal fetal monitoring, vaginal/perineal lacerations, operative delivery\(^2\)
  - Maternal injection-drug use\(^3\)

Interventions to Decrease Perinatal Transmission: Lessons from HIV?

- Elective cesarean delivery?
  - No randomized controlled trials
  - Meta-analysis of 8 studies including 641 mother-infant pairs show no change in transmission rate (Gharmar ME, et al. Arch Gynecol Obstet. 2011)

- Avoidance of breast feeding?
  - No increased transmission with breast vs. bottle feeding (Kumar RM, et al. J Hepatol. 1998)

- Avoidance of invasive procedures
  - Fetal scalp monitoring, amniocentesis, operative delivery
HCV Treatment Availability for Women and Children

No clear pathway to screen and treat women before they conceive

Before pregnancy

Pregnancy

Breast-feeding

Infancy

Childhood

>50% loss to follow-up of women and infants in the treatment cascade after delivery

• Source: Kushner T, et al. Hepatology Communications. 2018
Hepatitis C Treatment During Pregnancy?

**Arguments in Favor of Treatment**

- Treatment of Hepatitis C during pregnancy would reduce postpartum loss to follow-up by treating women at a time when they are engaged in prenatal care under insurance coverage
- Possible decrease in perinatal HCV transmission
- Children infected with Hepatitis C vertically develop cirrhosis at an earlier age than children who acquired infection through other routes during childhood, and are also at risk of acquiring hepatocellular carcinoma
- Surveys indicate the majority of women with Hepatitis C would be interested in Hepatitis C treatment during pregnancy if it could decrease perinatal transmission

**Arguments Against Treatment**

- Currently, there are few data on
  - Safety of Hepatitis C treatment in pregnancy
  - Safety of treatment in breastfeeding women

Harms of Evidence Gaps

- Historically, pregnant women were considered “vulnerable” because of the presence of a third party (the fetus) was unable to give consent.
- Pregnant women are often excluded from research participation, leading to harms:
  - Improper dosing
  - Unknown adverse consequences
  - Limited access to studies with direct benefit
The case for research in pregnancy

1) Pregnant women deserve EFFECTIVE treatment.
2) Pregnant women deserve SAFE treatment.
3) Pregnant women deserve EQUITABLE ACCESS to treatment.

Acknowledgement

- Launched in 2009
- Consortium of physicians, scientists and bioethics
  - Pregnant women no longer “vulnerable” in the US Code of Federal regulations and Common Rule
  - Support from professional societies (ACOG, SMFM)
  - Creation of Task Force on Research Specific to Pregnant and Lactating Women
First Study of Ledipasvir/Sofosbuvir in Pregnant Women

- Recruitment: October 2016 to October 2018
- Enrollment criteria
  - Hepatitis C-positive; 18–39 years of age
  - Enrollment at 23 to 24 weeks gestation
  - Singleton gestation without fetal anomalies
  - Non-genotype 2 or 3
  - No Hepatitis B, cirrhosis, or clinically significant drug use
  - Not at high-risk of spontaneous preterm birth

29 patients screened

- Screen fails (n=20)
  - Genotype 2: 5 patients
  - Genotype 3: 5 patients
  - Ongoing drug use: 4
  - Declined participation: 3
  - Delivering at outside hospital: 2
  - Concern for cirrhosis: 1

9 enrolled: 23-24 weeks’

- 9 completed study medication and delivered
- 9 completed SVR assessment

9 infants enrolled

- 9 infants completed 1-year follow-up
- 9 infants completed SVR assessment

Chappell CA, Lancet Microbe, 2020
## Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Number (%) or Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31 (25, 38)</td>
</tr>
<tr>
<td>White Race</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Military</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&gt;High school</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>High School</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>&lt;High School</td>
<td>2 (22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Use</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>Opioid Therapy</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Methadone</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Route of HCV acquisition</td>
<td></td>
</tr>
<tr>
<td>IV Drug Use</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Perinatal</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>HCV RNA &gt;6 million copies/mL at Enrollment</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>HCV Genotype 1</td>
<td>9 (100%)</td>
</tr>
</tbody>
</table>
HCV Viral Response to LDV/SOF During Pregnancy (HCV RNA copies/mL median [low, high])

All 9 mothers (100%) who have completed the SVR12 assessment achieved cure.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening</th>
<th>Enrollment</th>
<th>PK-1</th>
<th>PK-2</th>
<th>PK-3</th>
<th>Delivery</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>4.9 (1.7, 33.0)x10^5</td>
<td>5.2 (1.0, 73.5)x10^5</td>
<td>12 (0, 49)</td>
<td>0 (0, 12)</td>
<td>0 (0, 0)</td>
<td>0 (0, 12)</td>
<td>0 (0,0)</td>
</tr>
</tbody>
</table>
## Pregnancy and Delivery Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%) or Median (High, Low)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Related Adverse Events</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Maternal Related Adverse Events &gt;Grade 2</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vaginal Delivery</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks + days)</td>
<td>39+2 (36+6, 41+0)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,290 (2,600, 4,160)</td>
</tr>
<tr>
<td>Infant Length of Hospital Stay (days)</td>
<td>3 (2, 12)</td>
</tr>
<tr>
<td>Infant Related Adverse Events</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infant HCV RNA at Last Visit (copies/mL)</td>
<td>0 (0, 0)</td>
</tr>
</tbody>
</table>
Hepatitis C treatment in pregnancy: increased self-esteem and sense of well-being, which was sometimes protective against relapse

I’m down to like barely detectable... I think it’s definitely gonna help me not wanna keep relapsing or using because this has been such a process trying to cure it... that’s not the life I wanna live anymore, I don’t wanna use

“...Life-saving...”

I think I’m.. a bright thing and it’s a clean start...

I mean ecstatic, grateful. I don't know, kind of proud that I went through with something and accomplished it.

Conclusions from the Study

- In this first study of Ledipasvir/Sofosbuvir administration during pregnancy, there were no clinically significant changes in Sofosbuvir or Ledipasvir levels identified attributable to pregnancy.

- Ledipasvir/Sofosbuvir treatment started between 23-24 weeks of gestation was safe and effective, resulting in a 100% cure rate without any significant safety outcomes (N=9).

- Further studies should consider evaluation of pan-genotypic regimen for pregnancy (actively recruiting!)

- Larger studies must be conducted to confirm the safety and efficacy of Hepatitis C treatment during pregnancy.

Chappell CA, Lancet Microbe, 2020
Goal = Hepatitis C Elimination

- Substance use
- Poverty
- Trauma
- Mental Health Disorders
- Incarceration
- Poor social support

Test and Treat During Prenatal care