Hepatitis C and Pregnancy

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University of Utah
HCV AND PREGNANCY OBJECTIVES

- Epidemiology and Natural History
- Rates in Women of Child-bearing Age, Young adults and Children
- Pregnancy Impact and HCV
- HCV Screening recommendations including Universal screening
- Treatment
- Clinical trials for HCV in pregnancy
Epidemiology

• Approximately 3.5 million people in the United States are chronically infected with HCV (1.3%)\(^1,a\)
  – Including populations excluded from NHANES (e.g., the incarcerated, homeless, institutionalized, and those living on Native American reservations) brings the total estimate to 4.6 million\(^2\)

• Seroprevalence is higher in\(^1\)
  – 1945-1965 birth cohort (3.5%)
  – Non-Hispanic blacks (2.2%)
  – Males (1.9%) vs females (1.1%)

• Approximately 9% of all diagnosed individuals have been successfully treated\(^3,b\)

NHANES=National Health and Nutrition Examination Survey.
\(^a\)NHANES data as of 2010.
\(^b\)NHANES data, 2001-2008.

Prevalence of Chronic HCV in the United States

Analysis of NHANES HCV prevalence and National Vital Statistics System (NVSS)
HCV and narcotic deaths to calculate state-level HCV prevalence

- Estimated national prevalence of current HCV infection (RNA positive) = 1% (2.4 million persons)*
- Half of prevalent infections occur in 9 states and District of Columbia:
  - Alaska, Arizona, DC, Kentucky, Louisiana, New Mexico, Oklahoma, Oregon, Tennessee, and West Virginia

There is substantial variation in HCV prevalence among states, with the US west and Appalachian region containing more high-burden states

Rosenberg ES, et al. JAMA Network Open, 2018; 1(8); Rosenberg, AASLD 2018, 88

*Hofmeister, Hepatology 2018
HCV Genotypes by Geographic Region

HCV genotypes in the United States
- GT 1 is most common, accounting for ~78% of HCV infections\textsuperscript{2a}
- GT 1a subtype is twice as common as GT 1b

GT=genotype.
\textsuperscript{a}Derived from HCV RNA–positive participants in NHANES III conducted 1988 to 1994 (N=275).
\textsuperscript{1}World Gastroenterology Organisation. Diagnosis, management and prevention of hepatitis C. 2013.
Natural History of HCV Infection

Spontaneous clearance

Acute HCV infection

14%-46%

<1%

Fulminant hepatitis

54%-86%

Chronic hepatitis C

0.8% per year

Liver cirrhosis

15%-51%

Hepatocellular carcinoma (HCC)

1%-5% per year

Hepatic decompensation

3%-6% per year

Annual mortality rate of 2%-4% in CHC-infected patients with cirrhosis

a0.8% of those with CHC may develop HCC without having developed cirrhosis.

Changing Epidemiology of HCV in the US: Percentage of Newly Reported Cases by Age Group

California[^1]

2007

2015

Massachusetts[^2]

2002

2011


# Increasing HCV Burden in Young Adults in the US

## Population Totals

<table>
<thead>
<tr>
<th>Young adults &gt; Baby Boomers</th>
<th>Population Totals</th>
<th>Young Adult is on incline</th>
<th>Population Totals</th>
<th>Young Adults = Baby Boomers</th>
<th>Population Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennsylvania</td>
<td>12,784,227</td>
<td>California</td>
<td>39,250,017</td>
<td>Michigan</td>
<td>9,928,300</td>
</tr>
<tr>
<td>Ohio</td>
<td>11,614,373</td>
<td>Florida</td>
<td>20,612,439</td>
<td>Wisconsin</td>
<td>5,778,708</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>6,811,779</td>
<td>New York</td>
<td>19,745,289</td>
<td>Colorado</td>
<td>5,540,545</td>
</tr>
<tr>
<td>Indiana</td>
<td>6,663,053</td>
<td>Virginia</td>
<td>8,411,808</td>
<td>Connecticut</td>
<td>3,576,452</td>
</tr>
<tr>
<td>Kentucky</td>
<td>4,436,974</td>
<td>Washington</td>
<td>7,228,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arkansas</td>
<td>2,998,248</td>
<td>Arizona</td>
<td>6,931,071</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Mexico</td>
<td>2,081,015</td>
<td>Louisiana</td>
<td>4,681,666</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Virginia</td>
<td>1,831,102</td>
<td>Oregon</td>
<td>4,093,465</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maine</td>
<td>1,331,479</td>
<td>Iowa</td>
<td>3,134,693</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Dakota</td>
<td>757,952</td>
<td>Utah</td>
<td>3,051,217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vermont</td>
<td>624,594</td>
<td>South Dakota</td>
<td>865,454</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>51,894,796</td>
<td>Total population</td>
<td>118,065,119</td>
<td>Total population</td>
<td>24,824,005</td>
</tr>
</tbody>
</table>

## 11 States have rates of HCV infection in young adults surpassing that of Baby Boomers

Fraction of US population – 76%; Total population 20-39 = 66,249,672; Total females 20-39 = 32,733,899

Morse, A et al Making the case for universal screening for pregnant women for hepatitis C; one state at a time. Gastroenterology May 2018 Vol 154 (6)
Rates of HCV are Increasing in Women of Child-bearing Age

Number of reported cases of HCV infection among women aged 15-44 years and 45-64 years in the United States, 2006-2014.

Among women 15-44:
- Acute cases increased 3.4 fold
- Past or present cases increased 2 fold
- In 2013, rates surpassed older women

Centers for Disease Control and Prevention, National Notifiable Surveillance System, HCV, Hepatitis C virus
Gilead
Changing HCV Prevalence Among Pregnant Women

- During 2009–2014, HCV infection present at the time of delivery among pregnant women from states reporting HCV on the birth certificate increased 89%, from 1.8 to 3.4 per 1,000 live births.
- The highest infection rate in 2014 (22.6 per 1,000 live births) was in West Virginia; the rate in Tennessee was 10.1.  

1. MMWR / May 12, 2017 / Vol. 66 / No. 18
2. MMWR . 65(28):705-10, 2016 Jul 22
Gilead Pharmaceuticals
HCV Rates are Increasing Amongst Pregnant Women in the US

- Hospital discharge data from the Nationwide Inpatient Sample, the largest all-payer hospital inpatient care database in the US provides nationally representative estimates.
- Pregnancy hospitalizations with the following diagnoses were identified:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2002 through 2004</th>
<th>2005 through 2007</th>
<th>2008 through 2010</th>
<th>Total</th>
<th>Rate^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate^a</td>
<td>n</td>
<td>Rate^a</td>
<td>n</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>11,740</td>
<td>0.85</td>
<td>13,902</td>
<td>0.97</td>
<td>14,022</td>
</tr>
<tr>
<td></td>
<td>39,664</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>17,114</td>
<td>1.25</td>
<td>24,687</td>
<td>1.72</td>
<td>28,567</td>
</tr>
<tr>
<td>Gallbladder disease/cholelithiasis</td>
<td>59,341</td>
<td>4.32</td>
<td>65,748</td>
<td>4.59</td>
<td>67,850</td>
</tr>
<tr>
<td>Liver disorders of pregnancy^b</td>
<td>82,066</td>
<td>5.97</td>
<td>96,082</td>
<td>6.71</td>
<td>119,505</td>
</tr>
<tr>
<td>Chronic and alcohol-related liver disease</td>
<td>2758</td>
<td>0.20</td>
<td>4100</td>
<td>0.29</td>
<td>5714</td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>14,552</td>
<td>1.06</td>
<td>22,423</td>
<td>1.57</td>
<td>32,371</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>10,854</td>
<td>0.79</td>
<td>12,340</td>
<td>0.86</td>
<td>16,171</td>
</tr>
<tr>
<td></td>
<td>39,365</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For hepatitis C, there were significant increases in the rates for 2005 through 2007 and 2008 through 2010 compared to the referent time period (2002 through 2004)

HELPP, hemolysis, elevated liver enzymes, low platelet count.

^a Per 1000 pregnancy hospitalizations;
^b Includes acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, icterus gravis pregnancy, necrosis of liver of pregnancy, and hepatorenal syndrome following delivery.

Increasing Prevalence of Hepatitis C among Hospitalized Children Is Associated with an Increase in Substance Abuse

A. Sidney Barritt IV MD, MSCR 1, Brian Lee MPH, PhD 2, Thomas Runge MD, MPH 3, Monica Schmidt MPH, PhD 3, Ravi Jhaveri MD 4, 5

A: Hepatitis C Hospitalizations

B: Substance Abuse Hospitalizations
Global Call for HCV Elimination

- WHO vision: “A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable, and effective treatment and care”

- **Feasible** by scaling up key interventions:
  - Hepatitis B vaccination and treatment
  - Safe injection practices and safe blood
  - Harm reduction for PWID
  - Safer sex (including condom promotion)
  - Hepatitis C cure

- **US HBV/HCV Elimination Strategy** developed by National Academies of Sciences, Engineering, and Medicine: “elimination” = 90% reduction in incidence by 2030


Slide credit: clinicaloptions.com
US Progress Toward HCV Elimination Goals

- 12 countries are currently on track to achieve 2030 HCV elimination goals:
  - Australia, Egypt, France, Georgia, Iceland, Italy, Japan, Mongolia, the Netherlands, Spain, Switzerland, and United Kingdom
  - The United States is NOT among them
    - We are missing in important population for elimination efforts by not expanding treatment further to PWID population

http://polarisobservatory.org/polaris_view/hepC.htm

Slide credit: clinicaloptions.com
Reflexive HCV RNA Testing Overcomes the Gap in Confirming Chronic HCV Infection

**Step 1**
HCV screening test: detects HCV antibodies

**Step 2**
HCV diagnostic test: detects HCV RNA

**Step 3**
Evaluation and monitoring Care and treatment

Reflex HCV RNA testing of antibody-positive samples makes this 1 step
Recommended Testing Sequence for HCV Screening and Diagnosis

- **HCV antibody test**
  - Nonreactive
    - **No HCV antibody detected**
      - STOP
  - Reactive
    - **HCV RNA test**
      - Not detected
        - No current HCV infection
      - Detected
        - Current HCV infection
          - Link to care
        - Additional testing as appropriate

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**Notes:**

- For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.
- To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
- Adapted from CDC. *MMWR.* 2013;62:1-4.
Universal Screening

HCV in Pregnancy

Testing

<table>
<thead>
<tr>
<th>Recommendation for Universal Hepatitis C Screening in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECOMMENDED</strong></td>
</tr>
<tr>
<td>All pregnant women should be tested for HCV infection (see Recommendations for Initial HCV Testing and Follow-Up), ideally at the initiation of prenatal care.</td>
</tr>
<tr>
<td><strong>RATING</strong></td>
</tr>
<tr>
<td>IIb, C</td>
</tr>
</tbody>
</table>
Cost-effectiveness and Impact of Hepatitis C Virus Screening of Pregnant Women in the United States

Impact of HCV Chronic Prevalence on ICERs of Screening Pregnant Women Compared to No Screening

- Screening the estimated 5.04 million pregnant women in 2018 would result in detection and treatment of an estimated 33,000 women.
- Screening of pregnant women was cost-effective in settings with chronic prevalence among pregnant women at or above 0.05-0.08%.
HCV & Pregnancy – The Future…..

• **Universal screening** – near future nation wide
  – UUMC – July 1, 2019

• **Treatment** during pregnancy – a bit down the road
Transmission

- 1% to 2.5% of pregnant women are infected with HCV

- Mother-to-child HCV transmission (MTCT) ~ 5%
  - overall rate is estimated between 5-10%. - risk exists and is not on the radar of many providers
  - Higher viremia may increase risk of vertical transmission
    - in utero
    - Peripartum

- MTCT rates in co-infection with HIV carries a 10% risk
Impact of Pregnancy in HCV

- Down-regulation of maternal immune response
  - ↓ALT
  - ↑HCV RNA

- Antifibrotic effects of estrogens = beneficial impact in pregnancy

- Spontaneous viral clearance should be considered in post partum period when being assessed for treatment
Impact of HCV on Pregnancy Outcomes

• Poor birth outcomes:
  – Fetal growth restriction
  – Low birth weight (LBW)
  – Congenital anomalies
  – Preterm delivery
• Gestational DMs
• Feeding difficulties
• Adverse neonatal outcomes
  – Cephalohematoma
  – Brachial plexus injury
  – Fetal distress
  – Intraventricular hemorrhage
  – Neonatal seizures
Impact of HCV on Pregnancy Outcomes

• Intrahepatic cholestasis of pregnancy (ICP)
  – Overall incidence: 0.2% - 2.0%
  – 20 folds higher the HCV-infected pregnant women

• HCV + Cirrhosis + pregnancy = high risks of bleeding and death
Considerations

• Invasive testing: Counsel about risks of vertical transmission
  – Amniocentesis is recommended over chorionic villus sampling
• Internal fetal monitoring, prolonged rupture of membranes and episiotomy should be avoided
• Modes of delivery: C-section is **not** recommended for sole indication of HCV
• Breastfeeding should **not** be discouraged
<table>
<thead>
<tr>
<th>Pregnancy Considerations</th>
<th>Studies; # of Women</th>
<th>Number of Women</th>
<th>Strength of Evidence</th>
<th>Summary of Findings</th>
<th>SMFM Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective C-section versus vaginal delivery</td>
<td>4 cohort studies(^{(30,54-56)})</td>
<td>2,080</td>
<td>Low</td>
<td>No differences, but trends in opposite directions in highest-quality studies</td>
<td>Do not recommend C-section solely for indication of HCV</td>
</tr>
<tr>
<td>All C-section versus vaginal delivery</td>
<td>11 cohort studies(^{(24,27,31,57-64)})</td>
<td>2,308</td>
<td>Moderate</td>
<td>No association</td>
<td></td>
</tr>
<tr>
<td>Amniocentesis and CVS</td>
<td>3 cohort studies(^{(30,54,56)})</td>
<td>928</td>
<td>Insufficient</td>
<td>Inconsistent, but one good quality study (OR, 6.7; 95% CI, 1.1-36.0)</td>
<td>Counsel patients on potential risks of amniocentesis and CVS</td>
</tr>
<tr>
<td>Prolonged ROM</td>
<td>2 cohort studies(^{(30,31)})</td>
<td>245</td>
<td>Low</td>
<td>Yes with &gt;6 hours (OR, 9.3; 95% CI, 1.5-1.8)</td>
<td>Active labor management if prolonged ROM to expedite delivery</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>15 cohort studies(^{(24,27,30,31,54,55,59,62-69)})</td>
<td>2,971</td>
<td>Moderate</td>
<td>No association between breastfeeding and risk for transmission</td>
<td>Do not discourage breastfeeding based on positive HCV status</td>
</tr>
</tbody>
</table>

Babies Born to HCV Positive Women

- **Screening** (American Academy of Pediatrics and CDC rec)
  - Anti-HCV antibodies at >18 months or
  - HCV RNA on two occasions in infants > 1 month

- **Treatment**
  - Approved for children > 12yo
  - Ongoing trials, down to 3 yrs of age, with FDA approval soon
Improvements in HCV Treatment

- **Direct Acting Antivirals (DAAs)**
  - Glecaprevir/pibrentasvir (*Mavyret*)
    - x 8 weeks (16 weeks if cirrhotic)
  - Sofosbuvir/ledipasvir (*Harvoni*)
    - x 8 weeks
  - Sofosbuvir/velpatasvir (*Epclusa*)
    - x 12 weeks
HCV Can Be Cured

- Unlike HIV and HBV, HCV is curable\(^a\)
  - HCV RNA remains in the cytoplasm and does not integrate into host DNA\(^1\)
- HCV is highly genetically variable due to its:
  - High replication rate: On average, \(1.3 \times 10^{12}\) HCV virions are produced in each infected individual per day\(^2\)
  - High mutation rate: The HCV polymerase lacks a proofreading function and is error prone\(^3\)

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\(^1\) HBV=hepatitis B virus; HIV=human immunodeficiency virus; \(^a\)Cure, also known as SVR, is defined as no detectable HCV in the blood at 12 or more weeks after therapy is complete.\(^4\)

Treatment

- Antiviral therapies (DAAs) are not approved for use in pregnant women
- Abstain from alcohol
- Linkage to care for treatment
DAAs in Pregnancy

• Clinical trials with DAAs
  – Australia, large study with the use of epclusa x 12wk – ongoing
  – India, developing protocols
  – University of Pittsburgh/ Magee Womens Research Institute, safety and efficacy

• DAA pregnancy rating seems to be similar to antivirals (acyclovir, tenofovir)
  – Preclinical animal data does not support any notable toxicity
  – Wide pharmacokinetics range should not require dose change
A PHASE ONE STUDY OF LEDIPASVIR/SOFOSBUVIR IN PREGNANT WOMEN WITH HEPATITIS C VIRUS

Catherine A. Chappell, Elizabeth E. Krans, Katherine Bunge, Ingrid Macio, Debra Bogen, Kimberly K. Scarsi, Leslie A. Meyn, Sharon L. Hillier

Primary Objective
To define the safety of and virologic response to ledipasvir 90 mg-sofosbuvir 400mg (LDV/SOF) therapy in pregnancy

Hypothesis
Ledipasvir 90mg-sofosbuvir 400mg (LDV/SOF) therapy will be safe and effective in pregnant women

Study design
Started tx 23-24 weeks gestation, 9 enrolled, 8 completed therapy

Conclusion
100% of participants were cured of HCV and all infants are negative to date.
Summary

• Changing epidemiology of HCV
• Goal - Eradicate the virus
• Screening.
  – Family planning: screen before
  – Pregnancy: universal screening
  – Children: screen
• Impact the HCV cascade of care
CME

Pregnancy Care ECHO

Event code: **193126**

HCV ECHO

Event code: **193058**

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1. Dial **(801) 478-5852** from your CELL PHONE.
2. When prompted, enter the CME event code.