Hepatitis B and C
What Is New In Perinatal Transmission?

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Disclosure Statement

- I am a principal investigator or sub-investigator of multiple sponsored trials, but I do not receive any direct support from those companies.
Off Label Disclosures

• My presentation involves comments or discussion of unapproved or off-label, experimental or investigational use of hepatitis C anti-viral agents
Objectives

• Overview of implementation strategies to decrease hepatitis B perinatal transmission
• Describe the current knowledge of perinatal transmission of hepatitis C
• Discuss the potential rationale for treating pregnant women and their infants after vertical transmission
• Increase awareness about hepatitis C
HEPATITIS B
Case

- A baby in a rural KY nursery was born 6 hours earlier by uncomplicated vaginal delivery
- Mother’s HBsAg & HBeAg are positive and viral load (VL) is $10^6$
- Mother did not receive medications during pregnancy except PNV
- Mother does not want her baby to be immunized because her first child is “autistic due to vaccines”

What would you do?
Epidemiology

- 25000 babies born from HBsAg positive women
- 90% perinatal infections become chronic vs. 5% adult infections
- 1/3 chronic infections are transmitted from mother to child

Byrd K et al, Long S Principles of Ped Inf Dis, 2012
## Mother-to-Child Transmission

<table>
<thead>
<tr>
<th>Stage</th>
<th>Risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-embryonic and assisted reproductive therapy</td>
<td>Unknown</td>
<td>Theoretically possible</td>
</tr>
<tr>
<td>Prenatal- In utero</td>
<td>Low (&lt;3% of vertical infections)</td>
<td>HBeAg can cross the placenta</td>
</tr>
<tr>
<td>Intra-partum</td>
<td>70-90% if HBsAg &amp; HBeAg positive</td>
<td>Contact with mother’s blood or secretions</td>
</tr>
<tr>
<td></td>
<td>5-20% if HBsAg positive &amp; HBeAg negative</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>None</td>
<td>BF infants do not have increase rate in transmission</td>
</tr>
</tbody>
</table>

Nelson N et al. JPIDS, 2014
Mother-to-Child Transmission

High risk

- HBsAg + & HBeAg + (~90%)
- HBV VL ≥10⁶ to ≥10⁸ copies/mL
- If infection occurs during third trimester

Low risk

- HBsAg + & HBeAg - (~5-20%)
- HBV VL <10⁶ copies/mL
- Infection occurs during first or second trimester

Nelson N et al. JPIDS, 2014
Strategies to Reduce Transmission

- Maternal screening
- Universal vaccination
- Post-exposure prophylaxis (PEP)
  - Vaccination at birth
  - Immunoprophylaxis
- Antivirals
Screening

• Obtain HBsAg in all pregnant women at first prenatal visit
• Initiate vaccination if HBsAg negative and/or woman is unvaccinated
• Screen or re-screen at delivery if not screened or if the woman has risks factors*
• HBsAg positive test is reported in all states of the US

*Risk factors: household contacts or sex partners of HBsAg positive, injection drug users, ESRD, HIV, chronic liver disease, diabetes

CDC. ACIP MMWR, 2005
Prevention of Mother-to-Child Transmission

• Universal birth dose
  – Immunogenic
  – Decrease number of doses at 2 months
  – Increase likelihood of completion
  – Prefer within 24 hrs of birth

CDC. ACIP MMWR, 2005
Prevention of Mother-to-Child Transmission

Post-exposure prophylaxis

- Administer Hep B vaccine and Hep B immunoglobulin (HBIG) within 12 hours of birth
- Complete series within 6 months of birth

_CDC. ACIP MMWR, 2005_
Prevention of Mother-to-Child Transmission

Meta-analysis - effect of Hep B vaccine in newborns of positive HBsAg mothers

- Hep B vaccine decreased the risk of Hep B compared with placebo or no intervention (RR 0.28 95%CI 0.2-0.4)
- HBIG decreased the risk of Hep B compared with placebo or no intervention (RR 0.50 95%CI 0.4-0.6)
- Vaccination + HBIG vs. placebo or no intervention reduced Hep B (RR 0.08 95%CI 0.03-0.17)
- Recombinant vs. plasma derived vaccines; high vs. low dose vaccines; different vaccination schedules; and multiple vs. single HBIG did not reduce the risk of Hep B

Lee C et al, BMJ, 2006
Outcomes of Infants Born to Women Infected with Hep B

- Prospective study (2007-2013) using data from US funded perinatal prevention Hep B programs
- Analyzed 17951 mother-infants pairs
- HBsAg was available for 9252 (52%) infants
  - 1.1% acquired HBV infection perinatally
- 10760/11335 (95%) received Hep B vaccine and HBIG within 12 hours of birth

Outcomes of Infants Born to Women Infected with Hep B

- Factors associated with perinatal infection
  - Young maternal age (p 0.01)
  - Race - Asian Pacific Islander (p<0.01)
  - Maternal HBeAg positive (p<0.01)
  - Maternal HBeAg antibody negative (p<0.01)
  - Maternal VL ≥ 2000 IU/mL (p 0.04)
  - Non completion of vaccination series (p 0.01)
The recommendations seem straightforward but there is still a lot of work to do.
Baby’s birth weight > 2000 g

Mother HBsAg-positive

- Administer first dose of HepB vaccine and HBIG (separate sites) within 12 hrs of birth

Mother HBsAg-negative

- Administer first dose of HepB vaccine at hospital discharge (whichever comes first)

Mother’s HBsAg status unknown

- Administer first dose of HepB vaccine within 12 hrs of birth
- Obtain maternal HBsAg

At discharge:
- Provide mother with infant’s immunization record
- Emphasize importance of bringing record to pediatrician at each visit
- Educate mother about importance of completing infant’s vaccine series in 6 months
- Problem list should include exposed to viral disease (ICD9 V01.79 or ICD10 Z20.828)
- Vaccination series should be completed in 6 months (dose 2 at 1-2 months and dose 3 at 6 months of age)
- Post vaccination testing 1-2 months after completion
- Mother to follow up with public health department hepatitis B coordinator phone 502-574-6573

If maternal status is never known the infant should be followed as if born to HBsAg-positive mother, but HBIG should not be given
Prevention of Hepatitis B Transmission in Nursery and NICU

- Baby’s birth weight < 2000g
  - Mother HBsAg-positive
    - Administer first dose of HepB vaccine and HBIG (separate sites) within 12 hrs of birth
  - Mother’s HBsAg status unknown or maternal risk factors
    - Administer first dose of HepB vaccine within 12 hrs of birth
    - Obtain maternal HBsAg
    - Administer HBIG if maternal status will not be known within 12 hrs of birth
  - Mother HBsAg-negative and no maternal risk factors
    - Administer first dose of HepB vaccine at hospital discharge or 1 month after delivery (whichever comes first)

- Mother HBsAg-positive
  - Administer another dose of HepB vaccine one month after birth
  - Note: Birth dose does not count toward vaccine 3-dose vaccine series
  - At discharge:
    - Provide mother with infant’s immunization record
    - Emphasize importance of bringing record to pediatrician at each visit
    - Educate mother about importance of completing infant’s vaccine series in 6 months
    - Problem list should include exposed to viral disease (ICD9 V01.79 or ICD10 Z20.828)
    - Vaccination series should be completed in 6 months (dose 1 at 1 month, dose 2 at 2-3 months, and dose 3 at 6 months of age)
    - Baby’s post vaccination testing for HBsAg and HBsAb 1-2 months after the last dose in the series
    - Mother to follow up with public health department hepatitis B coordinator phone 502-574-6573

- Mother HBsAg-negative
  - Dose at birth does not count towards complete 3-dose vaccine series
  - Administer HepB vaccine
    - Dose 1 at 1-2 months of age
    - Dose 2 at 2-3 months of age
    - Dose 3 at 6 months of age

- If maternal status is never known the infant should be followed as if born to an HBsAg-positive mother
- Maternal risk factors included:
  - ≥ 2 sex partners in previous 6 months
  - STD
  - Injection drug use
  - HBsAg-positive partner
  - Clinical hepatitis
Post-Vaccination Testing

- Recommended for all infants born to HBsAg +
- Obtain HBsAg and anti-HBs
- 1-2 months after last vaccine dose ≥9 months
- 90% of infants that received PEP had protective levels
- If not protective levels a second Hep B series is given
- Long term protection is maintained in responding children

CDC. ACIP MMWR, 2005
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In 2008 post-vaccination testing was known for <60% of infants exposed

CDC. ACIP MMWR, 2005
HBV and Pregnancy

• Symptoms are indistinguishable from other types of hepatitis (most are asymptomatic)
• Gestational diabetes, antepartum hemorrhage and preterm labor (acute infection) are associated with HBV
• Rupture/bleeding of esophageal varices if cirrhosis
• High adrenal steroids & estrogen can increase VL
• Hepatic flare may occur at the end of pregnancy or postpartum
Management of HBsAg-Positive Pregnant Women

• No universal policy exits, but ACIP recommends
  – All HBsAg+ women should receive evaluation and treatment for chronic HBV infection
• Algorithms for liver disease assessment are similar for pregnant and non-pregnant women
  – Test for HBeAg, quantitative HBV DNA, and LFT’s
  – Results guide therapy and timing of intervention
  – Consensus recommendations
HBsAg+ Pregnant woman

1st trimester check:
- Hepatic panel, platelets, INR, HBeAb*, HBsAb, HBeAg, HBeAb, quantitative HBV DNA,
- Consider sequencing virus for primary resistance

If active disease/suspect cirrhosis — consider treatment with lamivudine, telbivudine, or tenofovir

End of 2nd trimester (at 26–28 weeks) check:
- ALT, quantitative HBV DNA

Previous child

No

Child HBV (-)

HBV DNA <200,000 IU/mL (10^6 copies /mL)

Monitor

HBV DNA >200,000 IU/mL (10^6 copies /mL)

Consider treatment with lamivudine, telbivudine, or tenofovir early in 3rd trimester (at 28–30 weeks)

Post-partum monitor for flare:
- Check ALT, quantitative HBV DNA at 1, 3, 6 months

Yes

Child HBV (+)

Regardless of maternal HBV DNA level

Consider stopping therapy post delivery **

* HBsAb: hepatitis B surface antibody
* HBeAb: hepatitis B e antibody

** discontinue therapy between 0 and 6 months—ideal time to discontinue remains unclear
Chronic Hepatitis B Treatment

- FDA approved 7 drugs
  - Category B: telbivudine, tenofovir
  - Category C: lamivudine, adefovir, entecavir
  - Category X: interferon (standard, pegylated)
Chronic Hepatitis B Treatment

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<td>216/7772 (2.5 %)</td>
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*Bzowej NH, Curr Hepatitis Rep, 2012*
Treatment during Pregnancy and Delivery

- Antiviral prophylaxis in late pregnancy if high VL is effective reducing transmission
- Recommended if
  - VL >10^5 copies/mL (>20000 IU/mL)
  - Evidence of liver disease
- Not recommended for immune tolerant or low VL
- Gaps on treatment: start, stop, flares, safety of BF while taking antivirals

Efficacy of Tenofovir

- HBsAg & HBeAg + with DNA >7.5 log 10 IU/mL at 30-32 wks
  - 62 received tenofovir (TNF)
  - 56 no treatment

- Maternal HBV DNA at delivery 4.3 (TNF) vs. 8.1; p<0.0001

- Infant HBV DNA positive at birth 6.2% (TNF) vs. 31.5%; p 0.0003

- Infant HBsAg positive at 6 mo 1.5% (TNF) vs. 10.7%; p 0.048

*Chen HL, Hepatology, 2015*
Efficacy and Safety of Telbivudine

- Prospective study from Feb 2008-Dec 2010
  - HBeAg positive (2nd or 3rd trimester)
  - 362 received telbivudine vs. 92 untreated
  - HBV DNA prior to delivery
    - 2.73 treatment group vs. 7.94 log_{10} copies/mL (p<0.001)
  - HBsAg positive at birth
    - 11.8% treatment group vs. 20.7%
  - HBV DNA at 7 months detected
    - 0% treatment group vs. 9.3% control (p<0.001)

- Treatment was safe

Han GR, J Viral Hep, 2015
Case

• A baby in a rural KY nursery was born 6 hours earlier by uncomplicated vaginal delivery
• Mother’s HBsAg & HBeAg are positive and viral load (VL) is $10^6$
• Mother did not receive medications during pregnancy except PNV
• Mother does not want her baby to be immunized because her first child is “autistic due to vaccines”

What would you do?
HEPATITIS C
Hepatitis C

- 3.2 million in US have chronic HCV infection
- 17000 new infections are diagnosed annually
- 0.6-2.4% of pregnant women are affected
- Perinatal transmission rate is 5-15%
- In USA 70% of all HCV isolates are genotypes 1a & 1b
- Before 1992 the most common cause of HCV transmission in children was
Hepatitis C

- 3.2 million in US have chronic HCV infection
- 17000 new infections are diagnosed annually
- 0.6-2.4% of pregnant women are affected
- Perinatal transmission rate is 5-15%
- In USA 70% of all HCV isolates are genotypes 1a & 1b
- Before 1992 the most common cause of HCV transmission in children was blood transfusion
- After implementation of universal testing of blood products, the most common source of transmission in children is vertical
Case

- 32-year-old G4P3 pregnant woman comes in labor
- Her HIV status is known to be positive from previous pregnancies
- She discloses regular IV drug use
- She lives in Austin, Indiana
What Is Particular About This Town?

*Rural Indiana Struggles to Contend With H.I.V. Outbreak*

**HIV Outbreak: Why Austin? Why Indiana?**

NEWS RELEASE, from Indiana State Health Commissioner Jerome M. Adams, MD, MPH 10:34 a.m. EDT May 19, 2015

How an HIV outbreak hit rural Indiana – and why we should be paying attention

With 150 cases is Indiana HIV outbreak reaching its peak?

So, what was the perfect storm here? Is Austin so different from other cities? Will it be the only small city to have to battle an HIV epidemic that's primarily due to intravenous drug use? Or is it the first?
What Is Particular About This Town?

HIV outbreak hit rural Indiana — and it’s changing its America

So, what was the perfect storm here? Is Austin so different from other cities? Will it be the only small epidemic that’s primarily due to injection first?
Aftermath
> 160 HIV infected and ~ 85% are co-infected with HCV
Perinatal Transmission

- Transmission rate is low → 5-15%
  - 50% of infants resolve infection → 3-5%
- HIV co-infection was a risk factor
  - 20-25% pre-HAART but rate is same now
- Mode of delivery does not affect transmission
  - Transmission at delivery or early in utero?
- Amniotic fluid is negative for HCV
- Discordant transmission in twins
- Peripheral blood mononuclear cell (PBMC) infection
- Past or ongoing maternal IV drug use
Transmission of Hepatitis C from Mother to Child

- 7698 women tested for Hep C antibodies
- 53 women HCV +
- 7 infants infected
Cohort 244 infants born to HCV + mothers
- 9/190 (5%) of those born to RNA + mothers were infected
- 0/54 of those born to RNA – were infected
- 3 infected infants resolved their infection
- Cohort 244 infants born to HCV + mothers
- 9/190 (5%) of those born to RNA + mothers were infected
- 0/54 of those born to RNA – were infected
- 3 infected infants resolved their infection

<table>
<thead>
<tr>
<th>Maternal characteristic</th>
<th>Infants, no. (%)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV RNA level, genome copies/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10⁶</td>
<td>61 (33.5)</td>
<td>1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;10⁶, &lt;10⁷</td>
<td>87 (47.8)</td>
<td>2 (2.3)</td>
<td></td>
</tr>
<tr>
<td>≥10⁷</td>
<td>34 (18.7)</td>
<td>4 (11.8)</td>
<td></td>
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<tr>
<td><strong>Age at delivery, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>100 (55.3)</td>
<td>5 (5.0)</td>
<td>.46</td>
</tr>
<tr>
<td>&lt;30</td>
<td>81 (44.8)</td>
<td>2 (2.5)</td>
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<tr>
<td><strong>Prior pregnancies, no.</strong></td>
<td></td>
<td></td>
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<tr>
<td>&gt;4</td>
<td>73 (40.1)</td>
<td>2 (2.7)</td>
<td>.70</td>
</tr>
<tr>
<td>≤4</td>
<td>109 (59.9)</td>
<td>5 (4.6)</td>
<td></td>
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<tr>
<td><strong>ALT level at delivery, U/L</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;35</td>
<td>45 (24.7)</td>
<td>3 (6.7)</td>
<td>.37</td>
</tr>
<tr>
<td>≤35</td>
<td>137 (75.3)</td>
<td>4 (2.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of delivery</strong></td>
<td></td>
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<tr>
<td>Vaginal</td>
<td>151 (83.4)</td>
<td>6 (4.0)</td>
<td>1.0 (reference)</td>
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<tr>
<td>Elective cesarean</td>
<td>12 (6.6)</td>
<td>0 (0.0)</td>
<td>Undefined</td>
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<tr>
<td>Emergency cesarean</td>
<td>18 (9.9)</td>
<td>1 (5.5)</td>
<td>1.4 (0.2–11.1)</td>
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<tr>
<td><strong>Fetal monitoring</strong></td>
<td></td>
<td></td>
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<tr>
<td>Internal</td>
<td>16 (8.8)</td>
<td>3 (18.8)</td>
<td>.02</td>
</tr>
<tr>
<td>External</td>
<td>165 (91.2)</td>
<td>4 (2.4)</td>
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<tr>
<td><strong>Rupture of membranes before onset of labor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (24.7)</td>
<td>4 (8.9)</td>
<td>.06</td>
</tr>
<tr>
<td>No</td>
<td>137 (75.3)</td>
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<tr>
<td><strong>Duration of membrane rupture, h</strong></td>
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<tr>
<td>&lt;1</td>
<td>53 (29.1)</td>
<td>0 (0.0)</td>
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<tr>
<td>1–5</td>
<td>59 (32.4)</td>
<td>1 (1.7)</td>
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<td>40 (22.0)</td>
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<tr>
<td>≤6</td>
<td>84 (47.7)</td>
<td>2 (2.4)</td>
<td></td>
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<td>7–12</td>
<td>48 (27.3)</td>
<td>4 (8.3)</td>
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<tr>
<td>≥13</td>
<td>44 (25.0)</td>
<td>1 (2.3)</td>
<td></td>
</tr>
</tbody>
</table>
Cohort 244 infants born to HCV + mothers

9/190 (5%) of those born to RNA + mothers were infected

0/54 of those born to RNA – were infected

3 infected infants resolved their infection
Cohort 244 infants born to HCV + mothers
- 9/190 (5%) of those born to RNA + mothers were infected
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- 3 infected infants resolved their infection
Breast Milk and Perinatal Transmission

- HCV is detected in BM at levels 100-1000 times lower than in plasma
- Studies attributing transmission through BM did not exclude in utero or peripartum
- Clinical guidelines do not prohibit breastfeeding in women HCV infected
- Human milk lipases with antiviral activity against enveloped viruses
Figure 6. Hypothetical model for inactivation of HCV by human breast milk. Due to a disruption of the milk fat globular membrane (gray), milk lipases (red) get access to the triglyceride (TG) core (yellow). Following milk digestion free fatty acids (FA), monoglycerides (MG), and diacylglycerides (DG) are released. These are able to disrupt the viral envelope of HCV (schematic depiction, showing the glycoproteins E1 and E2 (blue), the viral envelope (yellow) and the capsid formed by the core protein (light blue), which protects the viral RNA). Abbreviation: HCV, hepatitis C virus.
Figure 1. Human breast milk reduces HCV infectivity
Pregnancy and HCV

- 12 HCV pregnant women compared with matched 12 HCV non pregnant
- 2 point biopsies done
- Pregnant had fibrosis score deterioration (42% vs. 8%)
- Pregnant had necroinflammatory deterioration (83% vs. 25%)

Fontaine H et al. Lancet, 2000
Pregnancy and HCV

- 12 HCV pregnant women compared with matched 12 HCV non pregnant
- 2 point biopsies done
- Pregnant had fibrosis score deterioration (42% vs. 8%)
- Pregnant had necroinflammatory deterioration (83% vs. 25%)

201 women received a survey regarding prior pregnancies, menopause and the use of contraceptives
- Rate of fibrosis was higher in post-menopausal and nuliparous
- Pregnancy may have a beneficial effect

Fontaine H et al. Lancet, 2000
Di Martino V et al. Hepatology, 2004
Pregnancy and HCV

• Women with chronic infection usually have uneventful pregnancy
  – 370 pregnant women with HCV infection
    • ALT was elevated in 56% during first trimester but only 7% during third trimester
    • ALT returned to elevated level 6 months after delivery in 54%

Conte D et al. Hepatology, 2000
HCV Resolution and Pregnancy

- Compared 10 HCV RNA + pregnant vs. 8 HCV RNA + non-pregnant
- All pregnant women had drop in HCV levels after delivery
- 2/10 pregnant became undetectable after delivery

- Compared 22 pregnant vs. 120 non-pregnant
- 2 pregnant patients lost their HCV RNA vs. 1 non-pregnant
  14% vs. 2% p=0.03

Lin HH et al. BJOG, 2000
HCV RNA & T Cell Surge

Drop is due to surge in HCV specific T-cells after delivery

Pregnancy and HCV

• Pregnancy complications (controlling for IV drug)
  – Infants are more likely to be low birth weight and SGA
  – Infants require more NICU care and mechanical ventilation
  – Women have increased risk for gestational diabetes
  – Increase preterm birth
Pregnancy Symptoms

• Viremia 2-26 wks – resolved by cellular immune response mediated by HCV-specific CD4 and CD8
• Chronic infection – exhausted phenotype
• Humoral response is generated but does not neutralize the virus
Management of HCV Infected Women and Their Children

European Pediatric HCV Network

**Table 1**

Does HCV infection satisfy the criteria for introduction of routine antenatal screening?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Evidence regarding HCV</th>
<th>Satisfied in the context of antenatal HCV screening?</th>
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<tr>
<td>The condition is an important public health problem</td>
<td>Global prevalence 3%; estimated antenatal prevalence in Europe 1–2.5% [4]</td>
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</tr>
<tr>
<td>The natural history is well understood</td>
<td>Natural history in children is poorly clarified [56]</td>
<td>No</td>
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<td>A safe, valid and reliable screening test is available which is acceptable to those being tested</td>
<td>Third generation ELISA assays have high sensitivity (98–100%) and satisfactory specificity (66–99%) [84–86] although low positive predictive value Available treatment is contra-indicated during pregnancy [87,88], no interventions available</td>
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<td>Treatment or an intervention of proven effectiveness is available</td>
<td>Positive result in pregnancy associated with considerable anxiety, no benefit of diagnosis during pregnancy as no interventions</td>
<td>No</td>
</tr>
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<td>The risk of harm, both physical and psychological, is less than the chance of benefit</td>
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European Pediatric HCV Network

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</table>

Universal screening of pregnant women is not recommended

Pembrey et al. J Hepatology, 2005
Guidelines for Screening

Screening is recommended in pregnancy if

- Exposure to blood and derivatives before 1990 (in developed countries)
- Past or current IV drug abuse
- Partner with history of drug abuse
- Multiple sexual partners
- Infection with Hep B virus or HIV
- Absence of prenatal care

Resti et al. Dig Liver Dis, 2003
Guidelines for Screening

• If positive screen antibody perform PCR quantitative by 3\textsuperscript{rd} trimester
• Avoid invasive procedures for antenatal diagnosis
• Vaginal delivery should not be discouraged
• Mothers should be encouraged to breast feed
• A mother who infected her first child is not at greatest risk of infecting the second

Resti et al. Dig Liver Dis, 2003
Guidelines for Screening

Screening is recommended in general if

- Risk behaviors: injection-drug use
- Risk exposures: hemodyalisis, tattoos, healthcare workers, mother HCV-infected, prior recipients of transfusions or organ transplant, inmates
- Other: HIV infection, unexplained chronic liver disease, solid organ donors
- Periodic testing if ongoing risks

www.hcvguidelines.org, 2015
Treatment Pregnant Women

**Rationale**

- Clear mother’s chronic HCV
- Prevent vertical transmission

**Efficiency**

- Women who will not likely resolve their viremia after delivery
- Women who have high risk of transmission
Treatment Pregnant Women

Rationale
• Clear mother’s chronic HCV
• Prevent vertical transmission

Efficiency
• Women who will not likely resolve their viremia after delivery
• Women who have high risk of transmission

Can we predict who will transmit HCV?
If we were to treat pregnant women, when? Who? And with what?
## Treat Every Woman

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV approach without 25% transmission rate</td>
<td>• Very expensive at current prices</td>
</tr>
<tr>
<td>• Most women will benefit of a sustained virologic response</td>
<td>• Would mandate active screening by OB</td>
</tr>
<tr>
<td>• Will prevent transmission that leads to chronic infection</td>
<td>• Expose 95% infants to treatment</td>
</tr>
<tr>
<td></td>
<td>– NNT is high</td>
</tr>
</tbody>
</table>
Treat According to HCV RNA

**Pros**
- Evolving HBV approach (tenofovir in high risk if HBV >10⁶)
- Less costly
- More efficient benefit to risk ratio

**Cons**
- Requires coordination of care
- Would miss some as threshold is not well defined
- Right time is questionable
Figure 1. Hepatitis C virus (HCV) RNA levels among mothers who transmitted HCV to their infants (■) and mothers who did not transmit (♦), by maternal HIV infection status.

Where do you draw the line?
Treat According to Other Risk Factors

Pros

• Would allow for more precise patient identification
• Even more efficient benefit to risk ratio
• Potentially less costly if patients easily identified

Cons

• Requires studies that prove a marker is reliable
  – Fibrosis is not easily determined during pregnancy
• May miss some
• Would require integration of screening and intervention with PNC

But what would that risk factor be?
IL28B as Risk Factor

- Since 2009, SNPs in IL28B gene are associated with SVR
- Predicted spontaneous clearance in adults
- Could it predict which mothers would transmit?

Table 4. Role of IL28B in HCV Vertical Transmission and Chronic HCV Infection in Viral Genotype 1 Infants

<table>
<thead>
<tr>
<th>Risk Factors/Infection Status</th>
<th>HCV Vertical Transmission</th>
<th>HCV Chronification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infected</td>
<td>Noninfected</td>
</tr>
<tr>
<td>n=74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother's IL-28B status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC (19)</td>
<td>7 (37)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Non-CC (55)</td>
<td>8 (15)</td>
<td>47 (85)</td>
</tr>
<tr>
<td>Child’s IL-28B status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC (25)</td>
<td>6 (24)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Non-CC (46)</td>
<td>9 (20)</td>
<td>37 (80)</td>
</tr>
</tbody>
</table>

IL28B does not predict HCV vertical transmission

Forget Pregnancy

**Pros**
- Avoids risks
- Simple
- Allows the women that would clear a chance to do it on their own
- Cheaper

**Cons**
- Misses opportunity
- Risk of dropping out of care after pregnancy
- Reinforces the notion that we are afraid to treat pregnant women
The Future

• Continue working toward option for treatment with collateral benefits
• We need to find better ways to predict transmission
• Enroll in trials in late pregnancy and support a pregnancy registry
• As the cost decreases, it is possible that in the future we will treat all HCV RNA+ (pregnant or not)
What should we do in the meantime?
Infant HCV

- Identification is challenging
- Maternal antibodies last for 12-18 months
- Detection of HCV RNA by NAAT might be done at 1st well child visit (1-2 months of age)
  - During the first year children can have intermittent episodes of viremia
Infant HCV

- Most labs have converted to real-time PCR-based assay
  - Improve sensitivity
  - No studies in HCV exposed infants
  - Re-test ~ 4-6 months
  - If both tests negative infant unlikely to be infected
What Is New?

• Current NICHD MFMU network study
  – Observational study of HCV in pregnancy
  – 14 sites to recruit 1800 women
    • 1200 HCV RNA positive
    • Controls are healthy, otherwise uninfected
  – Analysis of maternal risk factors
  – Infants follow up at 2-6 months and 18-24 months
    using HCV RNA and antibody

ClinicalTrials.gov/NCT01959321
Perinatal HCV Exposure Protocol

- Screen pregnant women with risk factors
- Obtain HCV RNA PCR at the end of pregnancy
- Add problem to problem list in discharge paperwork
- Referral to ID clinic is encouraged
- HCV PCR to be done at 1-2 months of age
- Repeat PCR at 4 months of age (chronological age)
- PMD may consider HepC antibody at 18 months of age – optional
- If HepC positive at any time refer to ID clinic
Case

- 32-year-old G4P3 pregnant woman comes in labor
- Her HIV status is known to be positive from previous pregnancies
- She discloses regular IV drug use
- She lives in Austin, Indiana

Screen mother for HCV, if positive report mother and neonate to HD and ensure proper follow up including PCR in the baby at ~ 2 months of age
Questions
Hepatitis B Serology

Acute infection with recovery

Chronic infection

Byrd K et al, Long S Principles of Ped Inf Dis, 2012
Prevention of Mother-to-Child Transmission

Bathing

• Skin contamination might increase the risk of transmission

• Skin contamination can present a risk for occupational exposure
Prevention of Mother-to-Child Transmission

Bathing

• Skin contamination might increase the risk of transmission

• Skin contamination can present a risk for occupational exposure
Prevention of Mother-to-Child Transmission

Bathing

- Skin contamination might increase the risk of transmission
- Skin contamination can present a risk for occupational exposure
# Neonatal Vaccination

<table>
<thead>
<tr>
<th>Status</th>
<th>Doses</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother HBsAg pos</td>
<td>1, 2, 6 months</td>
<td>HBsAg at 9-18 months If neg and HBsAb &lt;10mIU/mL repeat 3 dose series</td>
</tr>
<tr>
<td>Mother HBsAg unknown</td>
<td>1, 2, 6 months</td>
<td>HBsAg at 9-18 months If neg and HBsAb &lt;10mIU/mL repeat 3 dose series</td>
</tr>
<tr>
<td>Mother HBsAg neg</td>
<td>1, 2, and 6-18 months</td>
<td></td>
</tr>
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</table>
HBIG During Pregnancy

- Meta-analysis evaluated 37 RCT
- Multiple small doses of HBIG in late pregnancy
- All received PEP
- Results suggest decreasing transmission (but less efficient if VL ≥ 10^8 copies/mL)
- Mechanism of protection and optimal dose are unknown

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Shi Z, Int J Infect Dis, 2010
Figure 3. Pooled estimates of risk of hepatitis C virus (HCV) vertical transmission among children ≥18 months born to HCV antibody–positive and RNA-positive mothers, by maternal HIV serostatus

Benova et al. CID, 2014
Figure 3. Pooled estimates of risk of hepatitis C virus (HCV) vertical transmission among children ≥18 months born to HCV antibody–positive and RNA positive mothers, by maternal HIV serostatus.
Treatment of Pregnant Women

• Would avoid treating early in pregnancy to prevent teratogenicity
• May be able to compress into late 2\textsuperscript{nd} or early 3\textsuperscript{rd} trimester because most regimens are usually 12 weeks
• Some patients could get only 8 weeks
Guidelines for Follow Up

Recommended management of infants born of anti-HCV positive mothers

• Definition of perinatal HCV infection
  – Born to anti-HCV positive mother and any of the following
    • HCV RNA detected by PCR in at least 2 different samples during the first year of life
    • Anti-HCV positive after 18-24 months of life

Resti et al. Dig Liver Dis, 2003
Fig. 2. Recommended follow-up schedule for early diagnosis of infection in infants born to HCV infected women.
Treatment

- Pegylated-interferon + ribavirin x 24-48wks – 40-90% achieve sustained virologic response (genotype dep)
  - SQ administration (weekly), AE, growth arrest, lack of FDA approval (pregnancy/children)
- Boceprevir and Telaprevir (protease inhibitors approved in 2011) improved response rates to 60-80% for genotype 1
- Simeprevir – increase potency and fewer AE
- Sofosbuvir – HCV polymerase inh approved in 2013
  - Oral (w ribavirin), 12 wks, response rate 90%
Pediatric HCV

- Age and developmental stage of immune system or liver are important factors in resolution
  - About 50% of infected infants will resolve viremia and hepatitis
  - Same results in a cohort of children infected by blood products
- ~20% of children with vertically acquired HIV and HCV developed cirrhosis by the end of adolescence
Direct-Acting Antiviral Drugs

- Near universal response
- Costs will limit access
- Pregnant women and children will wait the longest
- Better understanding of risk factors for transmission and resolution of viremia will help guide therapy
- Testing methods require validation in infancy
Treat Infants

• We would like
  – Specific formulation for infants
  – Rapid decline in viral RNA
  – Abbreviated regimen if possible
  • 4 weeks vs. now 8-12 weeks
Infants Symptoms

- Infection is acute and almost always asymptomatic
- Episodic and later onset viremia
- Robust cellular response
- No evidence of negative effect on growth or development
- Elevation of LFT’s and high VL (1st year)
- Risk of cirrhosis in childhood 1-2%
TABLE 2. HCV-RNA and RIBA data of babies born to HCV-RNA-positive mothers

- * Infants who remained HCV-RNA-negative during follow-up.
- + Infants who were HCV-RNA-positive on one occasion.
- ++ Infants who were HCV-RNA-positive on at least two consecutive testing.

<table>
<thead>
<tr>
<th>Group</th>
<th>Birth</th>
<th>4 months</th>
<th>8 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
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<tbody>
<tr>
<td>A*</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B†</td>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C‡</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>+</td>
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Group A*: n = 30
Group B†: n = 22
Group C‡: n = 8

HCV, hepatitis C virus.

Ceci et al. JPGN, 2001
Vertical Transmission

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Ceci et al. JPGN, 2001
Pediatric HCV

**Figure 1.** Follow-up investigation of hepatitis C virus (HCV)-infected children by HCV polymerase chain reaction. +, Positive result; −, negative result.

The Future

• There is no appropriate formulation for infants …yet
  – Approve therapy for children > 3 years of age
  – Pediatric studies are underway for > 3 years old for
    new agents
    • We will need specific studies in infants and decide
      who to target
Treatment of Infected Children

Fig. 3. Recommended criteria for initiation and duration of combination treatment in children with chronic infection.

Pembrey et al. J Hepatology, 2005
Pediatric HCV Treatment

- No indication for treatment in younger children
  - Lack of symptoms
  - Slow fibrosis
  - Side effects
  - Poor efficacy

- Expected expansion of treatment indications with direct-acting antiviral drugs

Liver biopsy used to decide:
- Poor SVR
- High AEs
- Complicated administration

Eradication of HCV for some using Peg-IFN-Rib
Pediatric HCV Treatment

- No indication for treatment in younger children
  - Lack of symptoms
  - Slow fibrosis
  - Side effects
  - Poor efficacy

- Expected expansion of treatment indications with direct-acting antiviral drugs
  - High SVR
  - Low AEs
  - All oral dosing

Scale is shifted in favor of near universal treatment

DAAs

Progress to long-term complications

University of Louisville
Kosair Children's Hospital
Co-infection

- ~20% of children with vertically acquired HIV and HCV developed cirrhosis by the end of adolescence
- Rates of sustained viral response were very low
- Cohort = 50 patients mean age 20 (SD ± 4.5)
- CD4 788 (516-980)
- HIV-RNA levels <50 copies/ml in 88%
- Genotypes 1 (66%), 4 (21%), 3 (11%) and 2 (2%)
- 40/50 had liver fibrosis (progression occurs slowly)
- 15/50 received therapy but only 5/15 (33%) showed sustained virological response

Sainz-Costa T, et al. ESPID 2015, Germany. Abstract 885