Hepatitis B and Pregnancy

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New HBV Infections by Year: United States (1966-2006)

Taiwan Childhood Hepatoma Study Group: HBV Vaccination and Hepatocellular Carcinoma

Incidence of Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Year Period</th>
<th>Per 100,000 Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981-1986</td>
<td>0.70</td>
</tr>
<tr>
<td>1986-1990</td>
<td>0.57</td>
</tr>
<tr>
<td>1990-1994</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Mortality Due to Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Year Period</th>
<th>Per 100,000 Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981-1986</td>
<td>0.80</td>
</tr>
<tr>
<td>1986-1990</td>
<td>0.58</td>
</tr>
<tr>
<td>1990-1994</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Children 6-14 years of age in Taiwan.

### HBsAg+ Prevalence Among Refugees Entering the United States, 2006-2008

<table>
<thead>
<tr>
<th>Region</th>
<th>HBsAg (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>8.1</td>
<td>7.2-9.0</td>
</tr>
<tr>
<td>East</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>4.8</td>
<td>4.4-5.3</td>
</tr>
<tr>
<td>East</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Southeast</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>South central</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>2.6</td>
<td>1.6-4.2</td>
</tr>
<tr>
<td>South/Central America and Caribbean</td>
<td>1.8</td>
<td>0.9-1.2</td>
</tr>
<tr>
<td>Total</td>
<td>2.8</td>
<td>2.6-3.0</td>
</tr>
</tbody>
</table>

Treatment During Pregnancy: Two SEPARATE Issues

• Treatment for the woman’s benefit
  – Why treat NOW?
    • Woman’s health \(\rightarrow\) advanced disease
    • Already on therapy \(\rightarrow\) concern for flare
    • Concern for progression

• Prevention of transmission to infant
  – No clear AASLD guidelines on treatment
  – Risk/benefit of treatment in third trimester

AASLD, American Association for the Study of Liver Diseases.
Two Separate Issues in Women of Childbearing Age

- Maternal health
- Perinatal transmission
Treatment for Woman’s Benefit

- Scenario One: She has cirrhosis
  - Unlikely to conceive: incidence of pregnancy in cirrhosis —1 in 5950
  - High rates of spontaneous abortion, premature birth, and perinatal death
  - GI bleeding most common complication
  - Would likely benefit from treatment
  - Benefit of therapy likely outweighs risks

GI, gastrointestinal.
Treatment for Woman’s Benefit

- Scenario Two: She has already been on therapy
- What is risk of flare if you take her off?
### Off-therapy HBV Flares

<table>
<thead>
<tr>
<th>Nucleoside-naïve Subjects with ALT Elevations &gt;10 x ULN and 2x Reference</th>
<th>ETV (0.5 mg)</th>
<th>3TC (100 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+</td>
<td>4/174 (2%)</td>
<td>13/147 (9%)</td>
</tr>
<tr>
<td>HBeAg+</td>
<td>24/302 (8%)</td>
<td>30/270 (11%)</td>
</tr>
</tbody>
</table>

**a** Studies AI463022 and AI463027.

**b** Reference is the minimum of the baseline or last measurement at end of dosing. Median time to off-treatment exacerbation was 23 weeks for ETV-treated subjects and 10 weeks for 3TC-treated subjects.

BARACLUDE® (entecavir) Full Prescribing Information. Bristol-Myers Squibb: Princeton, NJ.

Treatment for Woman’s Benefit

• Scenario Three: You are concerned about progression of disease
  – Not likely over a short period of pregnancy
Perinatal Transmission of HBV: an Australian Experience

HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

HBV DNA Level and Perinatal Transmission of HBV

Third-trimester Use of 3TC Reduces Risk of Perinatal Transmission

Infant Outcomes at Week 52

- HBsAg+ patients: 18 (3TC) vs 39 (Control)
- Viremia: 20 (3TC) vs 46 (Control)
- Anti-HBs: 84 (3TC) vs 61 (Control)

\[ P = .014. \]
\[ P = .003. \]
\[ P = .008 \text{ vs control}. \]

3TC, lamivudine.

Treatment During Late Pregnancy

- Nonrandomized case-controlled study by woman’s decision for treatment
- 190 pregnant Asian women with HBeAg+ CHB and HBV DNA >6 log$_{10}$ copies/mL

95 No antiviral treatment as control group

95 telbivudine 600 mg/day

Safety f/u phase

Baseline (20-30 weeks of gestation)

Delivery

4 weeks after birth

28 weeks after birth

Serum HBV DNA

HBV serology

Liver function

Safety, clinical f/u Q4 weeks

M-I HBV DNA

HBV serology

Liver function

Birth defects and safety

M-I blood test

Birth defects and safety

M-I blood test

CHB, chronic hepatitis B; f/u, follow-up; M-I, mother-infant; TBV, telbivudine.

Han G et al., 61st AASLD; Boston, MA; October 29-November 2, 2010; Abstract 212. (Slide courtesy Calvin Pan, MD.)
Changes in HBV DNA Levels: Treated vs Untreated Pregnant Women

- **PCR-based assay; lower limit of quantitation = 500 copies/mL.**
- **Shanghai Kehua Bio-engineering Co, Ltd, China.**
- **PCR, polymerase chain reaction.**

The primary ITT analysis based on missing = failures.

ITT, intention-to-treat.

M-I Transmission Status:
TBV-treated Group vs Control Group

Infants in TBV group (n = 95)
Infants in untreated group (n = 92)

Percentage of Infants HBsAg+ with or without detectable DNA

<table>
<thead>
<tr>
<th>Time</th>
<th>TBV Group (n = 95)</th>
<th>Untreated Group (n = 92)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Birth</td>
<td>6.32</td>
<td>30.43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0</td>
<td>8.70</td>
<td>.003</td>
</tr>
<tr>
<td>ITT Analysis</td>
<td>2.11</td>
<td>13.04</td>
<td>.004</td>
</tr>
</tbody>
</table>

*The primary ITT analysis based on missing = failures.

ITT, intention-to-treat.

Risk Factors Associated With Perinatal HBV Infection Due to Immunoprophylaxis Failure

- Immunoprophylaxis failure rate
  - Overall: 4.9%
  - Maternal HBV DNA >6 log_{10} copies/mL: 5.7%

- Independent risk factor for vertical transmission of HBeAg positive mothers
  - Maternal HBV DNA levels

- Immunoprophylaxis failure occurred in a significant proportion of infants born to mothers with anti-partum hemorrhage, meconium-stained amniotic fluid, independently

# Antiviral Options for HBV: Pregnancy Category

## Category B
- Telbivudine
- Tenofovir DF

## Category C
- Interferon alfa
- Peginterferon alfa-2a
- Peginterferon alfa-2b
- Lamivudine
- Adefovir
- Entecavir

**Pregnancy category B:**
Animal studies do not indicate a risk to the fetus and there are no controlled human studies, or animal studies do show an adverse effect on the fetus but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.

**Pregnancy category C:**
Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women.
Antiretroviral Pregnancy Registry Study (www.APRegistry.com)

- Prospective, international exposure-registration study (1989-2013; n=14,035)
  - >80% of cases are from the US
  - CDC population-based birth defects surveillance system
- APR overall findings
  - Overall birth defect rate comparable to CDC population-based surveillance data (2.9% versus 2.72%)
  - No specific birth defect patterns detected

<table>
<thead>
<tr>
<th></th>
<th>1st Trimester</th>
<th>2nd/3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any antiretroviral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth defect rate</td>
<td>2.9 (2.5-3.4)</td>
<td>2.8 (2.5-3.2)</td>
</tr>
<tr>
<td>Exposures (n)</td>
<td>6057</td>
<td>7976</td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth defect rate</td>
<td>3.1 (2.6-3.7)</td>
<td>3.1 (2.6-3.7)</td>
</tr>
<tr>
<td>Exposures (n)</td>
<td>3966</td>
<td>4066</td>
</tr>
<tr>
<td><strong>Tenofovir DF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth defect rate</td>
<td>2.2 (1.5-3.2)</td>
<td>2.3 (1.5-3.2)</td>
</tr>
<tr>
<td>Exposures (n)</td>
<td>1219</td>
<td>1370</td>
</tr>
</tbody>
</table>

Numbers in parentheses are 95% CI.

First trimester:
Check HBsAg, Anti-HBc, Anti-HBs

HBsAg-, anti-HBs-  
Initiate maternal HBV vaccination series in high-risk individuals  
Infant receives vaccine at birth

HBsAg+  
Confirm HBsAg positivity; Check quantitative HBV DNA at baseline and at Week 28

Anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody.
Suggested Management of HBV Infection During Pregnancy (cont’d)

HBsAg+

Yes

HBV DNA >10^8 copies/mL

Refer for consideration for treatment with 3TC, TDF, or TBV at Week 32

Infant receives HBIG + HBV vaccine at birth

HBV DNA <10^8 copies/mL

May consider treatment if previous child HBV+.

CDC: HBV Vaccine Response Among Infants Born to HBsAg-Positive Mothers

- Infants born in the US to HBsAg positive mothers (2008-2013) (n=8654)
  - ≥3 doses of HBV vaccine, available anti-HBs results
- Cumulative vaccine response rate: 97%
  - Response to initial HBV vaccine series: 94.7%
  - Non-responders who responded to 2nd vaccine series: 94.8%
- Receipt of 4th vaccine dose improved vaccine response rate (adjusted OR: 0.50 P<0.01)

<table>
<thead>
<tr>
<th>Bivariate predictors of infant antibody response*</th>
<th>Response to Vaccine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th vaccine dose</td>
<td></td>
</tr>
<tr>
<td>Yes (P=0.01)</td>
<td>96.1</td>
</tr>
<tr>
<td>No</td>
<td>94.5</td>
</tr>
<tr>
<td>Vaccine timing after birth</td>
<td></td>
</tr>
<tr>
<td>&lt;12 hours (P=0.04)</td>
<td>94.9</td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>91.6</td>
</tr>
<tr>
<td>Timing of last vaccine dose</td>
<td></td>
</tr>
<tr>
<td>&lt;164 days (P&lt;0.001)</td>
<td>88.3</td>
</tr>
<tr>
<td>≥164 days</td>
<td>94.9</td>
</tr>
</tbody>
</table>

Enhanced Perinatal Hepatitis B Prevention Program.

*Anti-HBs ≥10 mIU/mL.
HBV Flares Postpartum

- 38 pregnancies in 31 chronic HBsAg+ women
  - 24 (63%) HBeAg+; 14 (37%) HBeAg-
- Significant increase in liver-disease activity was seen after delivery
  - Defined as 3x increase in ALT within 6 months of delivery
- 17 (45%) with exacerbations postpartum
- Median maximal ALT increase 4 x ULN
- None led to decompensation

ALT, alanine aminotransferase; ULN, upper limit of normal.
Elective Cesarian Delivery and Risk of Perinatal Transmission of HBV

Transmission of HBV Infection (7-12 Months of Age)

<table>
<thead>
<tr>
<th>HBsAg-Positive Mothers (n=673/240/496)</th>
<th>HBeAg-Positive Mothers (n=365/131/273)</th>
<th>Mothers With HBV DNA ≥6 log_{10} Copies/mL (n=319/115/238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
<td>Elective cesarian</td>
<td>Elective cesarian</td>
</tr>
<tr>
<td>3.4%</td>
<td>4.2%</td>
<td>6.3%</td>
</tr>
<tr>
<td>1.4%*</td>
<td>2.6%*</td>
<td>7.2%</td>
</tr>
<tr>
<td>7.6%</td>
<td>2.9%*</td>
<td>2.9%*</td>
</tr>
</tbody>
</table>

Retrospective, single-center, chart review study. All infants received standard HBV prophylaxis (2007-2011).

*P<0.05 versus vaginal delivery and emergency cesarian.

Conclusions

• Vaccination/immunoprophylaxis is the MOST important preventative strategy
• Perinatal transmission risk is greatest in those with high maternal viremia: HBV DNA >8 logs
• Third-trimester treatment may reduce the risk of HBV transmission, but data are limited