Viral Hepatitis and Pregnancy

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**Pregnant Woman:**

Initial Workup of Abnormal Liver Tests

- **Hepatocellular profile?**
  - AST/ALT

- **Biliary profile?**
  - Bili/Alk phos
    - Bilirubin +/- alk phos
    - Alk phos only
      - No further workup

- Viral hepatitis
  - Herpes
  - Medications**

**Note:** Other differential diagnosis to consider if clinically appropriate: AIH, Wilson Disease
Australian antigen described

1965: Plasma derived vaccine
1981: Recombinant yeast derived vaccine licensed
1986: WHO recommends universal childhood vaccination
1991: > 92% infants 19-35 mos. vaccinated
2004: Treatment during pregnancy
2016: HBV: Historical Perspective
WHO member states with HBV vaccination of newborns

<table>
<thead>
<tr>
<th>Chronic HBV prevalence</th>
<th>Number of Countries</th>
<th>Countries with HBV Vaccine in schedule</th>
<th>Countries with HBV Birth Dose in schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH &gt;8%</td>
<td>87</td>
<td>73 (84%)</td>
<td>38 (44%)</td>
</tr>
<tr>
<td>Intermediate 2-8%</td>
<td>62</td>
<td>56 (90%)</td>
<td>33 (53%)</td>
</tr>
<tr>
<td>Low &lt;2%</td>
<td>44</td>
<td>34 (77%)</td>
<td>10 (23%)</td>
</tr>
</tbody>
</table>

62 million/135 million births were in the high prevalence countries

MMWR 57(46);1249-1252
Global Burden of Disease Study 2010: Causes of Death From Chronic Liver Disease

Patients (%)

Global 2010

<table>
<thead>
<tr>
<th>Liver Cancer</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>45%</td>
</tr>
<tr>
<td>HCV</td>
<td>26%</td>
</tr>
<tr>
<td>ETOH</td>
<td>20%</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
</tr>
</tbody>
</table>

USA 2010

<table>
<thead>
<tr>
<th>Liver Cancer</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>16%</td>
</tr>
<tr>
<td>HCV</td>
<td>40%</td>
</tr>
<tr>
<td>ETOH</td>
<td>29%</td>
</tr>
<tr>
<td>Other</td>
<td>14%</td>
</tr>
</tbody>
</table>

Increase in liver cancer deaths (past 20 years):
Globally (from 1.25 to 1.75 million/year); USA (45,000 to 70,000/year).

# Maternal HBV Status and Outcome of HBV Infection in Infants

<table>
<thead>
<tr>
<th>Mother</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td>HBsAg</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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

Treatment to prevent perinatal transmission

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


<table>
<thead>
<tr>
<th>HBsAg+ pregnant women (N = 313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with detectable HBV DNA (n = 213)</td>
</tr>
<tr>
<td>Infants tested (N = 138)</td>
</tr>
<tr>
<td>HBsAg+ infants (n = 4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBeAg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (n = 122)</td>
</tr>
<tr>
<td>Low HBV DNA (n = 115)</td>
</tr>
<tr>
<td>High HBV DNA (n = 29)</td>
</tr>
<tr>
<td>Very high HBV DNA (n = 69)</td>
</tr>
</tbody>
</table>

HBV DNA (copies/mL)
- Low: <10^5
- High: 10^5 to 10^8
- Very high: >10^8
HBV DNA Level and Perinatal Transmission of HBV

2.9

6.6

8.5

Transmission Rate (%)

All Infants of HBV DNA+ Women

HBeAg+ Women

Maternal HBV DNA (copies/mL)

<10^5

10^5-10^8

>10^8

Third Trimester Use of Lamivudine in Women With High HBV Viral Load

Infant Outcomes at Week 52

High HBV viremia: >1000 mEq/mL. All babies received HBIG + HBV vaccine.
Treatment During Late Pregnancy

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

**94 No antiviral treatment as control group**

**135 telbivudine 600 mg/day**

- 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
- 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.
Third Trimester Use of Telbivudine and Prevention of Perinatal HBV Transmission

- Open-label prospective study (n=229 pregnant women with chronic HBV infection)
  - Week 20-32 of gestation
  - Infants received standard HBV prophylaxis
- Telbivudine reduced mother-to-child transmission of HBV
  - Well tolerated
  - No increase in pregnancy or delivery complications
  - No congenital deformities

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Telbivudine (n=135)</th>
<th>Control (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal HBV DNA (log₁₀ copies/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.10</td>
<td>7.98</td>
</tr>
<tr>
<td>Prior to delivery</td>
<td>2.44</td>
<td>7.82</td>
</tr>
<tr>
<td>Infants HBsAg(+) ± detectable HBV DNA (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 28 weeks</td>
<td>0%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*P ≤ 0.001 versus control.

Tenofovir and Pregnancy Treatment

Study Design

200 pregnant women with HBeAg positive and serum HBV DNA >200,000 IU/mL were randomized 1:1 to two groups

- Mothers received no antiviral treatment as the control group
- Mothers received TDF 300 mg

Randomization

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline at 30-32 weeks of preg</td>
<td>Delivery</td>
</tr>
<tr>
<td>Screened at 28 weeks of preg</td>
<td>All infants received HB Ig and vaccine</td>
</tr>
<tr>
<td>4 weeks after birth</td>
<td>All infants received HB Ig and vaccine</td>
</tr>
<tr>
<td>24 weeks after birth</td>
<td>All infants received HBV vaccine</td>
</tr>
<tr>
<td>28 weeks after birth</td>
<td>Primary endpoint analysis</td>
</tr>
</tbody>
</table>

* TDF 300mg was administrated by mouth daily. The adherence to the therapy was monitored by pill counts. Mothers who discontinued TDF therapy were followed with the schedule of every 4 weeks for 12 weeks or longer.
Maternal Median HBV DNA and ALT Levels (IQR)

- **HBV DNA Levels (log_{10} IU/mL)**
  - TDF
  - Controls

- **ALT Levels (U/L)**

**Key Points:**
- IQR, Interquartile range
- Pan, AASLD 2015, 209
Efficacy Assessment for Infants

MTCT Rates in the TDF-Treated Group vs. the Untreated Group

All infants received appropriate immunoprophylaxis. MTCT was defined as HBsAg(+) or detectable levels of HBV DNA at the infants’ age of 28 weeks.

- **Per protocol analysis**
  - TDF-treated group: 0/92
  - Untreated group: 6/88

- **Intention-to-treat analysis**
  - TDF-treated group: 5/97
  - Untreated group: 18/100

P-values:
- P=0.007
- P=0.013
- 18.0%
The Frequency of Birth Defects or Congenital Malformations

<table>
<thead>
<tr>
<th>Newborn Measurements</th>
<th>TDF Group (n=95)</th>
<th>Control Group (n=88)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth defects or malformation†</td>
<td>2 (2.11)</td>
<td>1 (1.14)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Torticollis</td>
<td>1 (1.05)</td>
<td>0 (0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Umbilical hernia</td>
<td>1 (1.05)</td>
<td>0 (0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>0 (0)</td>
<td>1 (1.14)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

† The frequency of congenital deformities or defects of infants in the TDF-treated group did not significantly differ from that in the non-treated group (2.11%, 95% CI: 1.01–4.09% vs. 1.14%, 95% CI: 0.33–3.03%, p=1.00).
## Maternal Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Adverse Events: n ( % )</th>
<th>TDF Group</th>
<th>Control Group</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any degree of ALT elevation during study period*</td>
<td>60 (61.9)</td>
<td>41 (41.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>ALT elevation occurred from baseline to PPW 4</td>
<td>16 (16.5)</td>
<td>22 (22.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ALT elevation occurred from PPW5 to PPW 28†</td>
<td>44 (45.4)</td>
<td>30 (30.0)</td>
<td>0.028</td>
</tr>
<tr>
<td>Severe ALT flare (&gt;10 × ULN)†</td>
<td>1 (1.0)</td>
<td>3 (3.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Creatine kinase elevation*</td>
<td>7 (7.2)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Anemia</td>
<td>0 (0)</td>
<td>3 (3.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Confirmed creatinine ≥0.5 mg/dL above baseline</td>
<td>0 (0)</td>
<td>1 (1.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Confirmed creatinine clearance &lt;50 mL/min</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* P values <0.05
† The upper limit of normal range for alanine aminotransferase is 40 IU/mL. Abbreviations: ALT, alanine aminotransferase; PPW, postpartum week; ULN, upper limit of the normal range; TDF, tenofovir disoproxil fumarate.
Antiviral Options for HBV: Pregnancy Category

<table>
<thead>
<tr>
<th>Category B</th>
<th>Category C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telbivudine</td>
<td>Interferon alfa</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>Peginterferon alfa-2a</td>
</tr>
<tr>
<td></td>
<td>Peginterferon alfa-2b</td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
</tr>
<tr>
<td></td>
<td>Adefovir</td>
</tr>
<tr>
<td></td>
<td>Entecavir</td>
</tr>
</tbody>
</table>

**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.
Prevalence of Birth Defects With NUCs: Antiretroviral Pregnancy Registry

- Antiretroviral Pregnancy Registry is a large ongoing database of many antiretroviral drugs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; trimester</th>
<th>Prevalence % (95% CI)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; trimester</th>
<th>Prevalence % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth defects in a general population&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>2.7 (2.7, 2.8)</td>
</tr>
<tr>
<td>LAM</td>
<td>142/4527</td>
<td>3.1 (2.6-3.7)</td>
<td>207/7244</td>
<td>2.9 (2.5-3.3)</td>
</tr>
<tr>
<td>TDF</td>
<td>58/2452</td>
<td>2.4 (1.8-3.0)</td>
<td>25/1191</td>
<td>2.1 (1.4-3.1)</td>
</tr>
<tr>
<td>ADV</td>
<td>0/48</td>
<td>-</td>
<td>0/0</td>
<td>-</td>
</tr>
<tr>
<td>ETV</td>
<td>2/58</td>
<td>-</td>
<td>0/2</td>
<td>-</td>
</tr>
<tr>
<td>LdT</td>
<td>0/10</td>
<td>-</td>
<td>0/9</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Centers for Disease Control and Prevention birth defects surveillance system (MACDP) 1989 through 2003.

Potential limitations of registries such as this should be recognized. The limitations include, but are not limited to, underreporting, differential reporting, underascertainment of birth defects, differential ascertainment of birth defects, and loss to follow-up.

Viral hepatitis: HBV

- HBV is screened in first trimester
- If positive for HBV:
  - Treatment for the woman’s benefit
    - Woman’s health → advanced disease
    - Already on therapy → concern for flare
  - Prevention of transmission to infant
    - AASLD guidelines on treatment
    - Risk/benefit of treatment in third trimester

AASLD, American Association for the Study of Liver Diseases.
Treatment for Woman’s Benefit

• Treat if the mother has severe underlying disease
  – 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 outweighs risks

GI, gastrointestinal.

Suggested Management of HBV Infection During Pregnancy

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

HBsAg+

Yes

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

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

Infant receives HBIG + HBV vaccine at birth

HBV DNA <10^6 copies/mL

\[\text{May consider treatment if previous child HBV+}.\]

Viral Hepatitis: HBV flares

- HBV
  - ter Borg 2008
    - 38 pregnancies in 31 chronic HBsAg+ women
    - Significant increase in liver disease activity was seen after delivery
    - Defined as 3x increase in ALT within 6 mos of delivery
    - 17 (45%) with exacerbations postpartum
    - Median maximal ALT increase 4 x ULN
BMD in Infants

• 74 infants tenofovir in late pregnancy vs 69 tenofovir-unexposed infants
• Bone mineral content at one month post delivery
• Tenofovir-exposed newborns did not differ from unexposed newborns
  — Mean gestational age (38.2 vs 38.1) length (−0.41 vs −0.18) or weight (−0.71 vs −0.48)
• The mean (standard deviation) BMC of tenofovir-exposed infants was 12% lower than for unexposed infants (56.0 [11.8] vs 63.8 [16.6] g; P = .002)
• The adjusted mean bone mineral content was 5.3 g lower (95% confidence interval, −9.5, −1.2; P = .013) in the tenofovir-exposed infants
• need for minimization of exposure and assessment and discussion of clear risk and benefit
Viral hepatitis: HCV

• Risk of **vertical transmission 3-10%**:  
  – Vertical transmission risk 19% if HIV/HCV
• Mode of delivery appears not to change risk
• Infant: Higher rate of spontaneous clearance
• Test infants with HCV RNA on 2 occasions between the ages of 2 and 6 months and/or test for HCV antibody after 15 mo
• Avoid fetal scalp monitoring and invasive testing
• Breast feeding - acceptable unless clear nipple trauma or abrasions
A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/-Ribavirin Adolescents and Children With Chronic HCV-Infection

- Ages Eligible for Study: 3 Years to 17 Years

- **Inclusion Criteria:**
  - Consent of parent or legal guardian required
  - Chronic HCV infection

- **Exclusion Criteria:**
  - Co-infection with HIV, acute hepatitis A virus, or hepatitis B virus
  - Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal hemorrhage)
  - Pregnant or nursing females
  - HCV Genotype 1 or 4: Treatment naive with or without cirrhosis and treatment-experienced without cirrhosis will receive LDV/SOF FDC for 12 weeks. Treatment-experienced with cirrhosis will receive LDV/SOF FDC for 24 weeks.
  - HCV Genotype 3: Treatment-experienced with or without cirrhosis participants will receive LDV/SOF FDC + RBV for 24 weeks.
Viral Hepatitis

- HAV
  - Intrauterine transmission rare
  - Fecal oral transmission at birth possible
  - Breastfeeding not contraindicated
Viral Hepatitis: HEV

• HEV
  – fecal-oral transmission
  – Infection during pregnancy in endemic areas
    • 60% develop ALF
    • 31% mortality
  – Non-endemic areas lower mortality
    • Possible differences in HEV genotypes
  – High rate of vertical transmission (80%)
    • Infant mortality 40%
  – Travel to endemic area: avoid water, uncooked fruit, vegetables, shellfish
  – HEV vaccine trials ongoing
Viral hepatitis: HSV

- Herpes simplex virus
  - HSV hepatitis 32/137 cases were in pregnant women
  - High mortality (39%)
  - Clinical picture: *anicteric* hepatitis
    - Very high transaminases and mild bilirubin
  - If clinical suspicion is high, consider acyclovir

Summary

- Viral hepatitis should be considered in any pregnant woman with abnormal liver tests
- HBV is still transmitted in high risk individuals
  - Up to 10% when maternal viral loads are high
  - Consideration for treatment in third trimester
  - Risks and benefits should be fully discussed
- HCV treatment not warranted during pregnancy