Perinatal Management of Chronic Hepatitis B

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Antepartum and Intrapartum Management
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Overview

- Background/Epidemiology
- Clinical features/Laboratory findings
- Transmission
- Antepartum Evaluation/Therapy
- Mode of Delivery/Labor Management
- Infant Immunoprophylaxis
- Breastfeeding/PP Maternal Management

Chronic Hep B Prevalence, 2006

Prevalence of Hepatitis B Surface Antigen
- High >8%
- Intermediate 2% – 7%
- Low < 1%

CDC 2016
http://wwwnc.cdc.gov

Disclosures

I have no industry affiliations.
Hepatitis B: Clinical Features

- Incubation period: Average 60-90 days
- Clinical illness (jaundice): <5 yo, <10%  
  ≥5 yo, 30%-50%
- Fulminant hepatitis: 1-2%
- Acute case-fatality rate: 0.5%-1%
- Chronic infection: <5 yo, 30%-90%  
  ≥5 yo, 2%-10%
- Premature mortality from chronic liver disease: 15%-25%
Hepatitis B: Clinical Features

- 50% of adults are asymptomatic
- Preicteric or prodromal phase: 3-10 days
  - Malaise, anorexia, nausea, vomiting, right upper quadrant abdominal pain, fever, headache, myalgia, skin rashes, arthralgia and arthritis, and dark urine
  - ~ 1-2 days before the onset of jaundice
- Icteric phase: 1-3 weeks
  - Jaundice, light or gray stools, hepatic tenderness and hepatomegaly (spleenomegaly is less common)
- Convalescence phase: weeks-months
  - Malaise and fatigue

Outcome of Hepatitis B Infection by Age of Infection

Acute HBV with Recovery

Chronic HBV

Symptomatic Infection

Chronic Infection

Infection by Age of Infection

Symptoms

HBeAg | anti-HBe

Total anti-HBc

HBsAg | IgM anti-HBc | anti-HBs

Weeks after exposure

Titer

Weeks after Exposure

Titer

Acute
(6 months)

Chronic
(Years)

HBeAg

HBsAg

Total anti-
HBc

IgM anti-HBc

Years
### Hepatitis B and D

- **Hepatitis D (delta)**
  - Exists only in setting of chronic HBV infection

- **Transmission of HDV**
  - Perinatal
  - Percutaneous exposures: Injecting drug use
  - Perimucosal exposures: Sexual contact

- **Co-infection with hepatitis D virus**
  - Severe acute disease
  - Low risk of chronic infection

- **Super-infection with hepatitis D virus**
  - Usually develop chronic HDV infection
  - High risk of severe chronic liver disease

### Interpretation of Hepatitis B Serologic Tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td>Immune due to vaccination</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Positive</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>Positive</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Negative</td>
<td>Four interpretations possible*</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

*Postvaccination testing, when it is recommended, should be performed 1-2 months following dose #3.
1. May be recovering from acute HBV infection.
2. May be transiently immune and the test is not sensitive enough to detect a very low level of anti-HBs in serum.
3. May be susceptible with a false positive anti-HBc.
4. May be chronically infected and have an undetectable level of HBsAg present in the serum.

### HBV - HDV Coinfection

**Typical Serologic Course**

- **Symptoms**
- **ALT Elevated**
- **IgM anti-HDV**
- **anti-HBs**
- **HDV RNA**
- **Total anti-HDV**

**Time after Exposure**

### HBV - HDV Superinfection

**Typical Serologic Course**

- **Jaundice**
- **Symptoms**
- **ALT**
- **Total anti-HDV**
- **HDV RNA**
- **HBsAg**
- **IgM anti-HDV**

**Time after Exposure**
**Chronic Hepatitis B and Pregnancy Course**

- Pregnancy overall well tolerated
  - Not associated with adverse pregnancy outcomes
  - **Exception:** women with cirrhosis at risk
    - IUGR, intrauterine infection, PTB, IUFD
    - Gestational HTN, abruption, peripartum hemorrhage, death
- Viral reactivation and disease exacerbation may occur in pregnancy and postpartum
  - Viral load generally remains stable
  - Underlying liver disease may worsen, but progression to cirrhosis is rare
  - **Flares with serious clinical sequelae UNCOMMON**
  - Risk of flare greater after discontinuation of tx PP

**Hepatitis B Perinatal Transmission**

**Concentration of Hepatitis B**

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low/Not Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
<td>semen</td>
<td>urine</td>
</tr>
<tr>
<td>serum</td>
<td>vaginal fluid</td>
<td>feces</td>
</tr>
<tr>
<td>wound exudates</td>
<td>saliva</td>
<td>sweat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>breastmilk</td>
</tr>
</tbody>
</table>

**HBV Transmission**

- **Sexual**
- **Parenteral**
- **Perinatal**
  - **In-utero/transplacental=** rare
  - **Intrapartum=** predominant
Perinatal Transmission of HBV

- Perinatal Transmission
  - <10% if HBeAb+
  - 15% if HBsAg+
  - 70-90% if HBsAg+ and HBeAg+
    - 85-90% of infected infants → chronic HBV carriers
    - 25% of carriers die of CLD
- Timing of transmission
  - Majority of cases = intrapartum
  - Intrauterine infection (~5-10%): risk factors
    - HBeAg+ (and/or high maternal VL) OR 17.1
    - Preterm labor OR 5.4
    - Invasive genetic testing in setting of high maternal VL
    - Cirrhosis

Perinatal Transmission of HBV and Infant Immunoprophylaxis

- Infant vaccine and HBIG failure
  - HBeAg+ mothers with high VL (10^8 copies/mL)
  - Overall 3% transmission in viremic mothers
  - 7% in viremic HBeAg+ mothers
  - 9-39% in viremic mothers with VL ≥ 10^8 copies/mL
- Antiviral therapy before delivery to lower maternal viral load to further prevent perinatal transmission

Evaluation of HBV in Pregnancy

- Universal HBsAg screening
- If HBsAg positive:
  - LFTs, HBeAg, HBV DNA at onset prenatal care
    - Precore mutant: HBeAg negative but viremic!
  - Others: HBsAb, HBeAb, HBcAb, Hep D Ab, Hep E Ab
  - Platelets, INR
  - Consult with GI/Hepatology
    - 40% of OB providers did not refer HBsAg+ patients to specialist (Institute of Medicine)
  - HAV and HCV panel → HAV VAX if non-immune
  - Household/sexual contacts testing/immunization
  - RUQ US if h/o perinatally acquired, if HIV+, abnormal LFTs
  - Repeat LFTs and HBV DNA by 26-28 weeks

Ko 1994; Grosheide 1994; Alexander 1999; Towes 2001; Yi 2014
Consideration of Therapy for Chronic Hepatitis B in Pregnancy

- Active maternal disease (severe)/cirrhosis
  - Initiate Tx at onset of pregnancy evaluation
- High hepatitis B viral load ( > 6-8 log10 copies/mL or > 5 log 10 copies/mL and elevated LFTs)
  - Initiate Tx at 28-32 weeks
- Previous child infected with hepatitis B
  - Initiate Tx at 28-32 weeks
- Two most commonly used agents in pregnancy
  - Lamivudine- higher risk of resistance in long-term tx
  - Tenofovir- low risk resistance in long-term tx, 1st line

Hepatitis B Therapies

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Mechanism</th>
<th>Pregnancy Category</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>Nucleotide Analogue</td>
<td>B</td>
<td>300 mg PO daily</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Nucleoside Analogue</td>
<td>C</td>
<td>100 mg PO daily</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Nucleoside Analogue</td>
<td>C</td>
<td>0.5-1.0 mg PO daily</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Nucleotide Analogue</td>
<td>B</td>
<td>10 mg PO daily</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Nucleoside Analogue</td>
<td>B</td>
<td>600 mg PO daily</td>
</tr>
</tbody>
</table>

Antiretroviral Pregnancy Registry Data

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Earliest trimester of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st trimester birth defects/live births</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>60/2608 (2.3%)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>1434566 (3.1%)</td>
</tr>
<tr>
<td>Adefovir</td>
<td>0/48</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>0/10</td>
</tr>
<tr>
<td>Entecavir</td>
<td>2/58 (3.4%)</td>
</tr>
<tr>
<td>Any HBV nucleoside/ nucleotide*</td>
<td>2057290 (2.8%)</td>
</tr>
</tbody>
</table>

**Lamivudine and HBV Prevention Meta-Analysis**

- 10 RCTs; 951 HBV-carrier mothers
- Newborns: immunoprophylaxis at birth
- Mothers: lamivudine from 24-32 weeks until delivery-1 month PP
- Lamivudine group newborns
  - 13 to 24% lower incidence of in-utero infection, with HBsAg (P=0.04) and HBV DNA (P<0.001)
  - 1.4%-2% lower MTCT rate at 9-12 months, with HBsAg (P<0.01) and HBV DNA (P<0.001)

Shi 2012, Shi 2010

**Telbivudine and HBV Prevention**

- 60 HBV-carrier mothers
  - 30 treated, 30 untreated
  - Tx initiated 28-32 weeks until 30 days PP
  - Tx group VL reduced significantly
    - 7.38 log10 to 4.08 log10 (P<0.01)
- Newborn infection rate
  - All received immunoprophylaxis (vaccine, HBIG)
  - 0% in treatment vs. 13.3% in untreated group
  - 7 months

Zhang 2009

**Cost-Effectiveness of Maternal Therapy for Perinatal Prevention**

- Lamivudine or HBIG in 3rd trimester
  - Lamivudine: for each 100 HBsAg + pregnant women treated, 9.7 cases of chronic HBV infections prevented
    - Cost-savings of $5,184 and 1.3 life-years gained per patient treated
  - HBIG: for each 100 HBsAg + pregnant women treated, 9.5 cases of chronic HBV infections prevented
    - Cost-savings of $5,887 and 1.2 life-years gained per patient treated
  - Lamivudine and HBIG are cost-saving among wide range of assumptions

Unal 2011

**Hepatitis B Invasive Diagnostic Procedures during Pregnancy**

- 60 HBV-carrier mothers
  - 30 treated, 30 untreated
  - Tx initiated 28-32 weeks until 30 days PP
  - Tx group VL reduced significantly
    - 7.38 log10 to 4.08 log10 (P<0.01)
- Newborn infection rate
  - All received immunoprophylaxis (vaccine, HBIG)
  - 0% in treatment vs. 13.3% in untreated group
  - 7 months

Zhang 2009
Invasive Diagnostic Procedures

- Women undergoing amniocentesis with HBV
  - 63 infants with amniocentesis vs. 198 matched controls without amniocentesis
  - All infants received HBV vaccination and immunoglobulin
- Maternal viral load stratification
  - $>10^7$ copies/mL vs. lower
- Increased risk of in-utero transmission
- 50% vs 4%; OR 21.3; P=0.006
- Counseling for amniocentesis
  - Maternal-fetal transmission may increase with high maternal HBV viral load

Mode of Delivery and Hepatitis B

- Observational study; n=301
- All mothers HBsAg +
- 144 NSVD, 40 forceps/vacuum, 117 C-S
- All neonates received HBIG and HBV vax
- No difference in neonatal HBsAg by delivery mode
  - NSVD: 8.1%
  - Forceps/vacuum: 7.7%
  - Cesarean delivery: 9.7%

Wang Chin Med J 2002
Management of HBV Exposed Infant

- HBIG to infant @ birth
- HBV vax @ birth, 1-2 mos, and 6 mos
  - 65-96% efficacy
- HBIG + vax effectiveness
  - 85-95% at preventing chronic HBV
  - 60-90% if high maternal HBV VL (≥ 10^8)

Hepatitis B Breastfeeding and Postpartum Management

Breastfeeding and Hepatitis B

- Hepatitis B surface Ag found in breastmilk
  - Much lower levels than serum
- No apparent transmission to infants
  - Even before HBV vaccine available for exposed infants
- Observational study: n=369
  - 101 breastfed; 268 formula fed
  - No differences in maternal HBeAg or LFT abnl
  - Neonatal infection by 9-15 months of age (HBsAg +)
    - 0% breastfed vs. 3% formula fed
- Prevent bleeding from cracked nipples

Breastfeeding and Antivirals

- Limited data on safety of lamivudine or tenofovir and breastfeeding
  - No significant adverse outcomes reported thus far
- Nucleos/tide analogs secreted in breast milk
- Generally not recommended due to lack of data
  - Because tenofovir is administered as a prodrug, it may be preferred in nursing mothers who desire to breastfeed
**Postpartum and Antiviral Considerations**

- Long-term safety data are lacking
- Potential risks to the mother
  - Development of antiviral resistance (relatively unlikely, if drug of short duration and high barrier to resistance)
  - Increased risk for flare of hepatitis after treatment withdrawal
- Postpartum flare
  - 42% in those who did not receive antiviral therapy in pregnancy
  - 62% in those who had been treated and then discontinued therapy at delivery

Ter Borg 2008

**PP Maternal Management**

- Unclear when to discontinue therapy
- Active disease/cirrhosis
  - Continue therapy
  - Counsel regarding breastfeeding and antivirals
- Treated in 3rd trimester
  - Discontinue between 0-6 months PP (0-1 month PP)
    - Lamivudine greater resistance if used >6 months
    - Breast feeding – stop treatment after delivery
  - Counsel about breastfeeding and antivirals
  - Monitor for flare with LFT’s and HBV VL ~Q month x 6 mo
- Low VL and not treated
  - Monitor for PP flare with LFT’s and HBV VL at 1, 3, 6 mo

**Summary: Management of HBV in Pregnancy**

- Universal HBsAg screening
- If HBsAg positive:
  - LFTs, HBeAg, HBV DNA
  - HBsAb, HBeAb, HBcAb, Hep D Ab, Hep E Ab, Plt, INR
  - Consult with GI; household/partner testing/immunization
  - HAV and HCV panel → HAV VAX if non-immune
  - Tenofovir (1st line) if high viral load or prior + infant
  - HBIG + HBV vaccination to infant within 12 hours of birth
  - Trial of labor and “standard obstetric management”
  - Breastfeeding NOT contraindicated
  - Monitor for flare during PP and possibly pregnancy

**Resources**

- Centers for Disease Control and Prevention
  - [www.cdc.gov](http://www.cdc.gov)
- Society of Maternal-Fetal Medicine
  - [https://www.smfm.org](https://www.smfm.org)
- Advisory Committee on Immunization Practice
  - [http://www.cdc.gov/niP/ACIP/default.htm](http://www.cdc.gov/niP/ACIP/default.htm)
  - [www.hivandhepatitis.com](http://www.hivandhepatitis.com)
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