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

Disclosures

I have no industry affiliations.
**Hepatitis B Virus**

- Small, double-shelled virus
- Hepadnaviridae family
- Small circular DNA genome that is partially double-stranded
- Numerous antigenic components
  - HBsAg, hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg)
- Humans are the only known host
- Resilient virus
  - Infectious on surfaces for > 7 days at room temp

www.cdc.gov/vaccines/pubs

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**Prevalence Hepatitis B in US**

- Vaccine licensed
- HBsAg screening of pregnant women recommended
- Infant immunization recommended
- OSHA Rule enacted
- Adolescent immunization recommended

* Provisional date

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**Incidence of Hepatitis B in US**

- Incidence of acute Hepatitis B, by year
- United States, 1980-2009

www.cdc.gov/hepatitis
**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%

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**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 (splenomegaly is less common)
- Convalescence phase: weeks-months
  - Malaise and fatigue

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**Outcome of Hepatitis B Infection by Age of Infection**

![Graph showing percentage of chronic and symptomatic infections by age at infection](image)
### 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>Negative</td>
<td>Positive with &gt;10mIU/mL*</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>Positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM 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>Four interpretations possible¹</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>Positive</td>
<td>Four interpretations possible¹</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>Negative</td>
<td>Four interpretations possible¹</td>
</tr>
</tbody>
</table>

¹ Serological testing, when it is recommended, should be performed 1-3 months following dose #3.

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**Hepatitis B and D (Delta) Virus**

- **HBsAg**
- **δ antigen**
- **RNA**
**Hepatitis D: Transmission**

- Hepatitis D (delta) exists only in setting of chronic HBV infection
- Transmission
  - Perinatal
  - Percutaneous exposures
    - Injecting drug use
  - Permcusosal exposures
    - Sexual contact

**Hepatitis B and D**

- Hepatitis D (delta)
  - Exists only in setting of chronic HBV infection
- Transmission of HDV
  - Perinatal
  - Percutaneous exposures: Injecting drug use
  - Permcusosal 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

**HBV - HDV Coinfection**

- Typical Serologic Course
  - Symptoms
  - ALT Elevated
  - IgM anti-HDV
  - HDV RNA
  - HBsAg
  - Total anti-HDV

**HBV - HDV Superinfection**

- Typical Serologic Course
  - Symptoms
  - ALT Elevated
  - Total anti-HDV
  - IgM anti-HDV

- Jaundice
Chronic Hepatitis B and Pregnancy Course

- Pregnancy overall well tolerated
- Viral reactivation and disease exacerbation uncommon
- HBV DNA levels may even decrease after delivery in untreated women
- Risk of flare after discontinuation of tx PP

HBV Screening in Pregnancy

- Universal prenatal screening for HBsAg
- Only 35-65% HBsAg+ women identified when only “high-risk” screened

Hepatitis B Screening in Pregnancy

Hepatitis B Perinatal Transmission

CDC 2006, Baker 1999
### 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: risk factors
  - HBeAg+ OR 17.1
  - Preterm labor OR 5.4
  - Invasive genetic testing?
    - No difference in transmission in cases of amniocentesis

### 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**

Hepatitis B Evaluation and Therapy during Pregnancy

Evaluation of HBV in Pregnancy

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

Consideration of Therapy for Chronic Hepatitis B in Pregnancy

- Active maternal disease/cirrhosis
  - Initiate Tx at onset of pregnancy evaluation
- High hepatitis B viral load (VL $\geq 10^8$ copies/mL or $>10^5$ copies/mL and elevated LFTs)
  - Initiate Tx at 28 weeks
- Previous child infected with hepatitis B
  - Initiate Tx at 28 weeks
- Two most commonly used agents in pregnancy
  - Lamivudine- higher risk of resistance in long-term tx
  - Tenofovir- low risk of resistance in long-term tx

$^a$ In addition, measure HBcAb (at 6 months and every 6 months thereafter if positive and active hepatitis B is suspected.
$^b$ Discriminate therapy between 6 and 6 months—rival dose in discrimination results unclear.
Hepatitis B Therapies

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Mechanism</th>
<th>Pregnancy Category</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Nucleoside Analogue</td>
<td>C</td>
<td>100 mg PO daily</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Nucleotide Analogue</td>
<td>B</td>
<td>300 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>Lamivudine</td>
<td>99/3481 (2.8%)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>19/879 (2.2%)</td>
</tr>
<tr>
<td>Adefovir</td>
<td>0/37</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>0/5</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0/12</td>
</tr>
<tr>
<td>Any HBV nucleoside/nucleotide</td>
<td>118/4414 (2.7%)</td>
</tr>
</tbody>
</table>

Bzowej 2010

Lamivudine and HBV Prevention

- Antepartum HBIG or Lamivudine
  - RCT: 151 HBsAg+ pregnant women, nl LFTs
  - HBIG q4wks @ 28w gestation until labor
  - Lamivudine 100mg OD @ 28wk until PPD# 30
  - Control: no antepartum intervention
  - Intrauterine infection: neonatal HBsAg and/or HBeAg @ 24hr
    - HBIG 16%, Lamivudine 16% (p<0.05 vs. controls 33%)
  - 2 leg ↑ maternal HBV DNA before labor in HBIG and Lamivudine group
    - p<0.05 vs. controls
- Case series: 8 viremic pregnant ♀: Lamivudine 150mg OD x4wks
  - 12.5% transmission vs. 28% (untreated historical controls)
- Lamivudine @32 wks-4 wks PP in 114 women with HBV DNA >1000 Meq/mL
  - Infant with Pos HBsAg at week 52: Tx 18% vs. Control 39% (p=0.014)
  - Lost to f/u counted as failures
  - Tx 6% vs. Control 12% when calculating only those tested at 1 year
- Cases of vertical HBV transmission despite HBV suppression on Lamivudine
- Lamivudine + Tenofovir to prevent resistance?


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
**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

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**Hepatitis B and HIV Co-Infection**

- Combination ARV drug regimens including anti-hepatitis B drugs for all HIV-infected pregnant women with HBV co-infection
  - All pregnant women with HIV/HBV coinfection should receive a combination ARV drug regimen, including a dual NRTI/NtRTI backbone with two drugs active against both HIV and HBV
  - Tenofovir plus lamivudine or emtricitabine = preferred
dual NRTI/NtRTI backbone of a combination antepartum ARV regimen in HIV/HBV-coinfected pregnant women


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**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

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**Hepatitis B Mode of Delivery**
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% in setting of high maternal HBV VL (10⁸)

USPSTF 1996; Mele JID 2001

Hepatitis B Management of Exposed Infant

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

Breastfeeding and Antivirals

- Limited data on safety of lamivudine or tenofovir and breastfeeding
- Nucleos/tide analogs secreted in breast milk
- Generally not recommended
  - 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 short duration of therapy)
  - 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

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
**Hepatitis B Vaccination**

**Accelerated HBV Vaccination in Pregnancy**

- HBV vaccine IM at 0, 1, and 4 months
  - Versus 0, 1, and 6 months
- 200 high-risk pregnant women enrolled
- 84% completed 3-dose vaccine series
- Seroconversion after doses:
  - 1 dose=56% (95% CI, 49-63%),
  - 2 doses=77% (95% CI, 71-83%)
  - 3 doses=90% (95% CI, 85-94%)
- Body mass index was inversely associated with seroconversion rates (P<0.001)

**HBV Vaccination in Pregnancy**

- Considered safe in pregnancy
- Efficacy
  - 49% after 2 of 3 doses (HIV-neg pregnant women)
  - vs. 59-70% in non-pregnant
- Factors assoc with failure to seroconvert (pregnancy)
  - Smoking OR 7.5 (2.0-27.7)
  - BMI ≥ 34 OR 16.2 (1.7-154.7)
  - Age ≥ 25 yo OR 3.9 (1.1-14.4)
- Pre-test vaccination (anti-HBc Ab)
  - Cost-effective if prevalence > 20%
- Post-vaccination testing for certain groups
- Double dose in immunocompromised

**Summary: Management of HBV in Pregnancy**

- Universal HBsAg screening
- If HBsAg positive:
  - Consult with GI; household/partner testing/immunization
  - LFTs, HBsAg, HBV DNA
  - HBsAb, HBeAb, HBCAb, Hep D Ab, Hep E Ab, Plt, INR
  - HAV and HCV panel → HAV VAX if non-immune
  - Lamivudine or Tenofovir if high viral load or prior + infant
  - HBIG + HBV vaccination to infant
  - Trial of labor (avoid FSE??)
  - Breastfeeding NOT contraindicated
  - Monitor for flare PP
Resources

- Centers for Disease Control and Prevention
  - www.cdc.gov
- Advisory Committee on Immunization Practice
  - http://www.cdc.gov/nip/ACIP/default.htm
- www.hivandhepatitis.com
- http://aidsinfo.nih.gov/guidelines

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