The Evolving Landscape of Preventing Maternal-Fetal Hepatitis B Infections

Neil S. Silverman, M.D.
Center for Fetal Medicine and Women’s Ultrasound
Clinical Professor, Obstetrics/Gynecology
Division of Maternal-Fetal Medicine
David Geffen School of Medicine at UCLA
Disclosure

- I have no financial or other conflicts to disclose
Roadmap

- Magnitude of the problem
- Impact and severity of disease
- Availability and safety of current therapies
- Applicability of therapies to pregnancy: both maternal and fetal issues
Hepatitis B Prevalence in an Unregistered Prenatal Population
Implications for Neonatal Therapy

Neil S. Silverman, MD; Marilyn J. Darby, MD; Sheila L. Ronkin, MD; Ronald J. Wapner, MD

Study Objective.—To evaluate the risk and associated cofactors for hepatitis B infection in inner-city pregnant women not registered for prenatal care.

Design.—Fifteen-month survey of 208 patients not registered for prenatal care, compared with 1555 women registered for prenatal care during the same period.

Setting.—An urban university hospital prenatal clinic and labor unit.

Results.—Unregistered patients had a significantly higher rate of hepatitis B surface antigen positivity than patients who had registered with the clinic (6.7% vs 0.8%; P < .0001). Unregistered patients with positive results of urine drug screening (46%) had a relative risk for seropositivity of 29.2%, compared with registered patients who did not have histories of illicit drug use (95% confidence interval, 25.9% to 32.4%), while registered patients with past histories of drug use had a relative risk of 6.7%, compared with the reference group that did not have histories of drug use (95% confidence interval, 1.8% to 24.0%).

Conclusions.—Among inner-city pregnant women not registered for prenatal care, a positive result of urine drug screening is a rapidly available marker for increased risk of hepatitis B surface antigen positivity. Infants born to unregistered women with positive results of urine drug screening before maternal hepatitis B surface antigen results are available may warrant empiric initiation of hepatitis B virus–specific prophylaxis.
HBV: Epidemiology

- HBV infection remains a worldwide public health problem
- One-third of the world’s population (2 billion people) have been infected with HBV, with 360 million (18%) being chronic carriers
  - 45% of the world’s population live in high-endemic areas, with lifetime infection risk of >60%
  - Only about 12% of the world’s population live in low-endemic areas
- CHB is the most common cause of HCC: 50% of cases worldwide and 80% of cases in high-endemic areas
- HCC is the 6th most common cancer and the 3rd most common cause of cancer death in the world

HBV: Viremia and Disease

- Large prospective cohort (Taiwan): ↑ HBV-DNA (> 10^4 copies/mL) significantly associated with higher risks of cirrhosis, HCC, death, regardless of HBeAg status

  Chen CJ, JAMA 2006; Iloege UH, Gastroent 2007

- RCTs in patients with chronic HBV and fibrosis/cirrhosis showed benefit from antiviral rx on disease progression vs placebo
  - Progression ↓ over 32 months with lamivudine vs placebo (8% vs 18%, p = 0.01), but benefit reduced as resistance develops.  
    Liaw YF, NEJM 2004

- Rx with other nucleot(s)ide analogs (NAs)
  - Histologic improvement with lamivudine, adefovir, tenofovir
  - Sustained suppression of HBV-DNA without resistance during long-term entecavir rx → significant improvements and reversal of fibrosis/cirrhosis

  Chang TT, Hepatol 2010
Chronic HBV: Current Treatment Options

- 5 NAs and 2 interferons available
- Key changes in 2009 Practice Guidelines based on recent trials (Lok ASF, AASLD Guidelines, Hepatology 2009)

Tenofovir superior to adefovir after 48 weeks of therapy, with no resistance detected after 96 weeks of treatment

- Undetectable HBV-DNA: 76% vs 13% (results seen in both e-antigen (+) and (-) patients (Marcellin P, NEJM 2008)
- More recent study: no tenofovir resistance after 144 weeks of therapy in 426 patients monoinfected with HBV (Snow-Lampart A, Hepatology 2011)

FIRST LINE THERAPIES
- Tenofovir
- Entecavir
- Pegylated interferon
- Adefovir moved from 1st-line to 2nd-line
# HBV Antiviral Resistance Issues

<table>
<thead>
<tr>
<th>AGENT</th>
<th>RESISTANCE DATA</th>
<th>CLINICAL ISSUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>14-32% after 1 year&lt;br&gt;60-70% after 5 years</td>
<td>Higher resistance with:&lt;br&gt;- longer duration of rx&lt;br&gt;- higher baseline viremia</td>
</tr>
<tr>
<td>Adefovir</td>
<td>0-3% at 1-2 years&lt;br&gt;11-18% at 3-4 years</td>
<td></td>
</tr>
<tr>
<td><em>Entecavir</em></td>
<td>Virologic breakthrough rare in NA-naïve pts&lt;br&gt;Resistance 1-2% in naïve pts up to 5 yrs of rx&lt;br&gt;Resistance high (51%) in LAM-refractory pts</td>
<td>More potent than lamivudine and adefovir in vitro and in clinical trials</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>2-5% after 1 year&lt;br&gt;11-25% after 2 years</td>
<td>Less resistance than lamivudine, but increases dramatically after 1&lt;sup&gt;st&lt;/sup&gt; year</td>
</tr>
</tbody>
</table>
Cumulative annual incidence of resistance in patients who are NA-naive

HBV Infection and Pregnancy

- In the United States, an estimated 24,000 women with HBV infection give birth each year\(^1\)
- Women without prenatal care have higher rates of HBV carrier status\(^2\)
- Hepatitis B vaccination is the most effective measure to prevent HBV infection and its consequences

HBV Screening

- Screen all pregnant women, not just those in risk groups
  - If HBsAg (+) in 1st trimester (and no prior knowledge or history), re-test at 32-34 weeks to exclude the small group of asymptotically infected women who will clear infection

- Use prenatal testing as an opportunity to recommend screening and vaccination of family members

- Vaccine not contraindicated during pregnancy
General Recommendations for CHB Management

- Stress the importance of regular primary care; offer referral to a disease specialist.
- Screen for other infections (HIV and other STIs, hepatitis C virus) if the patient is at risk.
- Counsel the patient to reduce liver damage by avoiding alcohol and other hepatotoxins (eg, over-the-counter medications, traditional medicines).
- Recommend hepatitis A vaccine if the patient is susceptible (even during pregnancy).
Impact of Screening and Treatment on Perinatal Transmission

- At least 95% of pregnant women in US are screened for HBsAg before delivery
- Among infants at risk for HBV in US, 92% complete 3-dose vaccine series by age 3 \((Shepard \ CW, \ Epid \ Rev \ 2006)\)
  - Rate varies: 78% in LA to up to 98% in CA
- Perinatal transmission has declined in US over past 2 decades \((MMWR, \ 2006)\)
- Outside US, many high-prevalence countries lack newborn vaccination coverage
  - In 87 countries with HBV prevalence > 8%, infant vaccine coverage averages 36% \((MMWR, \ 2008)\)
Neonatal HBV Infection

- Perinatal (vertical) transmission is extremely efficient: 80-90% in absence of prophylaxis

- Of infected infants
  - 85-90% become chronic HBV carriers
  - 25% of carriers die from PHC or cirrhosis
  - 2-3% will develop acute fulminant hepatitis

- In both infants and adults, survivors of fulminant hepatitis rarely have chronic disease,
  - Low-load infection commonly produces chronic viremia after milder illness
Outcomes of Hepatitis B Virus Infection by Age at Infection

- **Chronic Infection (%):**
  - Birth: 80%
  - 1-6 months: 60%
  - 7-12 months: 40%
  - 1-4 years: 20%
  - Older Children and Adults: 0%

- **Symptomatic Infection (%):**
  - Birth: 0%
  - 1-6 months: 0%
  - 7-12 months: 0%
  - 1-4 years: 0%
  - Older Children and Adults: 100%
Neonatal HBV Prophylaxis: Passive vs Active Regimens

- HBIG alone
  - 20-25% of infants HBsAg (+) in first year
- Vaccine alone
  - 75% long-term efficacy
- HBIG and vaccine
  - 85-95% long-term efficacy
In Utero Infection Risks: HBeAg Status

- HBeAg a marker for active viral replication
  - Filtered through placenta: present in up to 70% of newborns, but only 10% of these are actually infected
    - Without viremia, almost all infants HBeAg (+) at birth are not @ 12 mos.

- Mechanisms for high rate of infectivity in infants born to HBeAg (+) mothers not entirely clear
  - HBeAg transferred to fetus may interfere with T-cell recognition
  - Detectable HBV-DNA in infant serum at birth is most important predictor for immunoprophylaxis failure

In Utero Infection Risks: Maternal Viremia

- Maternal HBV-DNA level most important predictor of MTCT
  - Earlier studies showed prophylaxis effective rate (PER) close to 100% if pre-labor levels < 5.5 log 10 copies/mL \(^1,2\)
  - Recent prospective studies in Asia showed stepwise decrease in PER as HBV-DNA levels rose above 6-8 log 10 copies/mL \(^3,4\)

- Large scale study in 1043 mother-infant pairs showed prophylaxis failures **only** in HBeAg(+) mothers, and directly related to viral load \(^3\)
  - Predelivery HBV-DNA:  
    - < 6 log 10 – failure 0%
    - 6.0-6.99 log 10 - 3.2%
    - 7-7.99 log 10 – 6.7%
    - ≥ 8 log 10 – 7.6%

- Maternal HBV-DNA level > 6 log10 copies/mL at delivery appears to be most important predictor of in utero MTCT and prophylaxis failure \((\text{Pan CQ et al, Clin Gastro Hepatol 2012})\)

---

Role of Maternal Viremia: Additional Recent Evidence

- 303 infants born to HBsAg (+) mothers from April 2007-March 2011 (single center, Taiwan)
  - 27% of mothers also HBeAg (+): they had higher viral loads: (7.4 ± 1.9 vs 2.7 ± 1.4 log 10 copies, p<0.0001)
  - 10 children chronically infected, all born to HBeAg (+) women with high VL (median 8.4, range 6.5-9.5 log 10 copies)
- Maternal viral load significantly associated with infection risk: **3.5 OR for each log 10 increase**
- Predictive infection rates:
  - 7 log 10: 6.6%, 8 log 10: 12.6%, 9 log 10: 27.7%

Clinical trials demonstrating efficacy of neonatal IP were conducted before the concept of viral load as a predictor of MTCT --- compare HIV.

HBV viral load is correlated with risk of MTCT and prophylaxis failure.
- **Residual 5-15% rate of infected infants despite neonatal prophylaxis**

Approaches to altering MTCT:
- In utero infection: antepartum treatment
- Intrapartum infection: route of delivery?

Using HIV as a model, reducing maternal viremia during pregnancy and delivery may address all 3 potential routes.
- **Avoiding maternal antiviral resistance needs to be a concern**
Antepartum Intervention: HBIG

- Early reports suggested that varying series of 3rd-trimester HBIG resulted in drops in maternal viremia with modest reduction in MTCT rates \(^1-3\)
- Recent large RCT showed that antepartum HBIG was not effective in preventing MTCT (Yuan J, J Viral Hepat 2006)
  - 250 HBeAg (+) pregnant women received HBIG at 1, 2, and 3 months before delivery
  - All newborns received standard immunoprophylaxis
  - No differences in maternal HBsAg or HBV-DNA levels after treatment, and no differences in newborn PER at 12 months
- Cochrane analysis: methodologic quality of studies “low” (Lee C, Cochrane 2006)
  - Also raised the concern for maternal risk of developing immune complex disease due to HBIG reacting with circulating HBsAg

Antepartum Antiviral Therapy: Lamivudine

- **Early treatment series (2000-2003)**
  - 3 women with high HBV-DNA levels treated in last 4 weeks of pregnancy, results compared with stored sera from 8 “control” infants\(^1\)
    - Treated mothers had 1-2 log drop at delivery; 0/3 children infected
  - 8 mothers treated in last month of pregnancy vs 24 historical controls\(^2\)
    - Infant immunization failure in 1/8 (12.5%) of treated vs 7/25 (28%) of untreated “controls”

- **1 Early trial: lamivudine vs HBIG vs placebo**
  - Lamivudine superior to HBIG or placebo in preventing immunization failure in infants born to highly viremic HBeAg (+) mothers

---

1. Van Nunen AB, J Hepatol 2000
2. Van Zonneveld M, J Viral Hepat 2003
3. Li XM, World J Gastroent 2004
Lamivudine RCT in Pregnancy

- Multicenter RCT, placebo-controlled (2009)
  - 155 highly viremic mothers (most > 9 log 10 copies/mL)
    - Treated from 32 weeks until postpartum
    - All newborns received immunoprophylaxis
  
- Results:
  - Strong effect on maternal viral load from lamivudine vs. placebo: mean ↓ by 2 log in active rx group
  - > 50% (p=0.014) reduction infant infection rates @ 1 yr followup (18 vs. 39%)
    - However, high followup loss rate: 31% in placebo group, 13% in lamivudine group
  - No neonatal safety effects noted, but 62% of women had ALT flares when lamivudine stopped 4 weeks postpartum

Lamivudine Meta-analysis

- 10 RCTs included (2003-2009): only 3 blinded and placebo-controlled, total of 951 women
  - Women treated from 24-32 weeks gestation to 4 wk PP
  - Newborns all received combined immunoprophylaxis
  - Lamivudine for prevention of IUI (based on HBV-DNA+)
    - OR = 0.22 (0.12 - 0.40); p < 0.001
  - Lamivudine for prevention of MTCT (9-12 mos)
    - OR = 0.2 (0.10 – 0.39); p < 0.001

- Conclusions:
  - Lamivudine effective for in utero and MTCT (late) transmission
  - No significant adverse effects or pregnancy impact

Other NAs to Interrupt HBV MTCT

Telbivudine (2011), 600 mg/day  (Han GR, J Hepatol 2011)
- Prospective open-label trial vs decliners as controls
- 135 HBeAg (+) women with HBV-DNA > 7 log10 copies/mL vs 94 controls (63% of study population had > 8 log 10 copies)
- Treated from 20-32 weeks through 4 weeks postpartum
- Results (90% retention)
  - Mean maternal HBV-DNA ↓ from 8.1 to 2.4 log 10 in rx group (vs 8.0 to 7.8)
  - MTCT rate ↓ with telbivudine: 2% vs 13% (p < 0.01)

- Observational series of 52 infants born to 50 women receiving telbivudine for CHB before or in early pregnancy, meds continued
  - 3.8% rate of congenital malformations (2 minor, including ear tags)
- All infants HBsAg (-) at 6 months post-delivery age
- 86% of women maintained virologic response (< 500 copies/mL)
Tenofovir to Interrupt HBV MTCT (1)

- Tenofovir (2012), 300 mg/day (Pan CQ. Dig Dis Sci, Apr 2012)
  - One case series of 11 women treated from 28-32 weeks (median 29 weeks) until delivery; no control group
  - Mean maternal HBV-DNA from 8.9 to 5.2 log 10 copies (p < 0.001)
    - 6/11 (55%) achieved < 6 log 10 copies/mL
  - All infants HBsAg (-) at 36 weeks post-delivery age
  - No maternal ALT flares after tenofovir stopped; 6 had 2-log rebound
Tenofovir to Interrupt HBV MTCT (2) -- 2016

- Expanded research project from prior group
  - 200 women with HBV DNA levels at least 200K IU/mL randomized to TDF (30-32 wks - 4 wks PP) or usual care
  - Median baseline levels $10^8$ IU/mL in both groups

- Maternal results
  - 68% in TDF group had viral levels < 200K at delivery, compared to 2% in control group ($p < 0.001$)
  - Mean level was 4.7 vs 8.0 log 10 (TDF v cont) ($p < 0.001$)

- Neonatal results
  - At PP week 28, infection rates were 5% vs 18% ($p=0.007$)

- Safety profiles not significantly ↑ in rx groups

Pan CQ et al (NYU/China). NEJM 2016 (June 16)
Is Testing and Treating for HBV Cost-Effective?

- 2 recent decision model analyses by CDC group: constructed for 2010 birth cohort of 4 million newborns
- Modeled to test 2 strategies, followed by maternal antiviral prophylaxis (lamivudine): 28 weeks - 4 weeks postpartum
  - Testing was either HBeAg or HBV load ≥ 10⁶-⁸ copies/mL
  - All newborns received active-passive immunoprophylaxis
- 1ˢᵗ study (2014): both testing strategies produced savings, prevented chronic HBV infections, and saved QALYs
  - HBeAg was more cost-effective than load of 10⁸ or 10⁶
  - But -- HBeAg had disadvantage of not being able to monitor response
  - May have more application in resource-poor areas
- 2016 analysis: authors included cost benefits of preventing perinatally-acquired chronic HBV using *tenofovir* as guided by viral load (vs rx cost during pregnancy) – favored viral load + rx

Recent Perinatal HBV Practice Guidelines (non-U.S)

2012: EASL (European Assn. for Study of the Liver)
- Mothers with HBV-DNA levels > 10^6-7 IU/ml should be informed that using an NA to reduce viral load could add to effectiveness of neonatal HBIG and vaccination
- Telbivudine, lamivudine, tenofovir as options

June 2013: UK National Institute for Health and Care Excellence (NICE)
- Discuss risks/benefits of antiviral therapy for mother and infants
- For maternal HBV-DNA > 10^7 IU/ml, offer tenofovir in 3rd trimester until 4-12 weeks after birth (unless mother meets criteria for long-term treatment)
Introduction
Obstetric providers are challenged continuously with the evaluation of the potential benefits and harms of new diagnostic and therapeutic procedures or treatments for patients (mother and fetus), often in the setting of limited high-quality data (e.g., from randomized clinical trials). The purpose of this document is to aid clinicians in counseling their patients regarding the risk.

Between 800,000-1.4 million people in the United States and more than 240 million people worldwide are infected with hepatitis B virus (HBV). Specific to pregnancy, an estimated prevalence of 0.7-0.9% for chronic hepatitis B infection among pregnant women in the United States has been reported, with >25,000 infants at risk for chronic infection born annually to these women. Vertical transmission of HBV from infected mothers to their fetuses or newborns, either in utero or peripartum, remains a major source of perpetuating the reservoir of chronically infected individuals globally. Universal screening for hepatitis B infection during pregnancy has been recommended for many years. Identification of pregnant women with chronic HBV infection has been encouraged to reduce the risk of perinatal transmission.

All authors and Committee members have filed conflict of interest disclosure delineating personal, professional, and/or business interests that might be perceived as a real or potential conflict of interest in relation to this publication. Any conflicts have been resolved through a process approved by the Executive Board. The Society for Maternal-Fetal Medicine has neither solicited nor accepted any commercial involvement in the development of the content of this publication.
### Summary of recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Perform routine screening during pregnancy for HBV infection with maternal</td>
<td>1A Strong recommendation,</td>
</tr>
<tr>
<td>HBsAg testing.</td>
<td>high-quality evidence</td>
</tr>
<tr>
<td>2 Administer hepatitis B vaccine and HBIG within 12 hours of birth to all</td>
<td>1A Strong recommendation,</td>
</tr>
<tr>
<td>newborns of HBsAg-positive mothers, or those with unknown or undocumented</td>
<td>high-quality evidence</td>
</tr>
<tr>
<td>HBsAg status, regardless of whether maternal antiviral therapy has been given</td>
<td></td>
</tr>
<tr>
<td>during the pregnancy.</td>
<td></td>
</tr>
<tr>
<td>3 In pregnant women with HBV infection, we suggest HBV viral load testing in</td>
<td>2B Weak recommendation,</td>
</tr>
<tr>
<td>the third trimester.</td>
<td>moderate-quality evidence</td>
</tr>
<tr>
<td>4 In pregnant women with HBV infection and viral load &gt;6-8 log 10 copies/mL,</td>
<td>2B Weak recommendation,</td>
</tr>
<tr>
<td>HBV-targeted maternal antiviral therapy should be considered for the purpose</td>
<td>moderate-quality evidence</td>
</tr>
<tr>
<td>of decreasing the risk of intrauterine fetal infection.</td>
<td></td>
</tr>
<tr>
<td>5 In pregnant women with HBV infection who are candidates for maternal</td>
<td>2B Weak recommendation,</td>
</tr>
<tr>
<td>antiviral therapy, we suggest tenofovir as a first-line agent.</td>
<td>moderate-quality evidence</td>
</tr>
<tr>
<td>6 We recommend that women with HBV infection be encouraged to breast-feed as</td>
<td>1C Strong recommendation,</td>
</tr>
<tr>
<td>long as the infant receives immunoprophylaxis at birth (HBV vaccination and</td>
<td>low-quality evidence</td>
</tr>
<tr>
<td>hepatitis B immunoglobulin).</td>
<td></td>
</tr>
<tr>
<td>7 For HBV-infected women who have an indication for genetic testing, invasive</td>
<td>2C Weak recommendation,</td>
</tr>
<tr>
<td>testing (eg amniocentesis or chorionic villus sampling) may be offered.</td>
<td>low-quality evidence</td>
</tr>
<tr>
<td>Counseling should include the fact that the risk for maternal-fetal</td>
<td></td>
</tr>
<tr>
<td>transmission may increase with HBV viral load &gt;7 log 10 IU/mL.</td>
<td></td>
</tr>
<tr>
<td>8 We suggest cesarean delivery not be performed for the sole indication for</td>
<td>2C Weak recommendation,</td>
</tr>
<tr>
<td>reduction of vertical HBV transmission.</td>
<td>low-quality evidence</td>
</tr>
</tbody>
</table>

HBIG, HBV immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Guidelines

The recommendations in this document reflect the national and international guidelines related to hepatitis B infection during pregnancy.
Summary

- HBV remains a global public health issue, with perinatal transmission a major source of infection.
- Neonatal immunoprophylaxis protocols have dramatically decreased rates of MTCT for HBV.
- Antepartum anti-HBV therapy to reduce maternal viremia before delivery holds promise for decreasing immunization failure rates due to intrauterine infection.
- Tenofovir (and entecavir) may prove to be the optimal candidate(s) for further study and use for this indication, due to their more favorable resistance profiles.