The Evolving Landscape of Preventing Maternal-Fetal Hepatitis B Infections

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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

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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 carriers¹
  - 45% of the world’s population live in high-endemic areas, with lifetime infection risk of >60%²
  - Only about 12% of the world’s population live in low-endemic areas²
- CHB is the most common cause of HCC: 50% of cases worldwide and 80% of cases in high-endemic areas²,³
- HCC is the 6th most common cancer and the 3rd most common cause of cancer death in the world⁴

Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- ≥8% - High
- 2-7% - Intermediate
- <2% - Low
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>
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<tr>
<th>AGENT</th>
<th>RESISTANCE DATA</th>
<th>CLINICAL ISSUES</th>
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<tbody>
<tr>
<td>Lamivudine</td>
<td>14-32% after 1 year 60-70% after 5 years</td>
<td>Higher resistance with: - longer duration of rx - higher baseline viremia</td>
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<tr>
<td>Adefovir</td>
<td>0-3% at 1-2 years 11-18% at 3-4 years</td>
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<td>* Entecavir</td>
<td>Virologic breakthrough rare in NA-naïve pts Resistance 1-2% in naïve pts up to 5 yrs of rx Resistance high (51%) in LAM-refractory pts</td>
<td>More potent than lamivudine and adefovir in vitro and in clinical trials</td>
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<tr>
<td>Telbivudine</td>
<td>2-5% after 1 year 11-25% after 2 years</td>
<td>Less resistance than lamivudine, but increases dramatically after 1st year</td>
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<tr>
<td>* Tenofovir</td>
<td>2 pivotal trials: no resistance after 96-144 wks of rx, despite low rates of viral breakthrough</td>
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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 (e.g., over-the-counter medications, traditional medicines)
- Recommend hepatitis A vaccine if the patient is susceptible
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
Outcome of Hepatitis B Virus Infection by Age at Infection

- **Symptomatic Infection** (%):
  - Birth: 0%
  - 1-6 months: 0%
  - 7-12 months: 0%
  - 1-4 years: 0%
  - Older Children and Adults: 0%

- **Chronic Infection** (%):
  - Birth: 100%
  - 1-6 months: 80%
  - 7-12 months: 60%
  - 1-4 years: 40%
  - Older Children and Adults: 20%
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.
    - Detectable HBV-DNA in infant serum at birth is most important predictor for immunoprophylaxis failure

- 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

- With postnatal immunoprophylaxis, MTCT transmission rarely occurs from HBeAg (-) mothers

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%

Maternal Approaches to Reducing HBV MTCT?

- Clinical trials demonstrating efficacy of neonatal IP were conducted before the concept of viral load as a predictor --- 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 > 2 log 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

  - 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

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 (1)

- **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)
Other NAs to Interrupt HBV MTCT (2)

- **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
Cumulative annual incidence of resistance in patients who are NA-naive

Treating HBV During Pregnancy:
Safety Data from ARV Pregnancy Registry

(Brown RS, et al. J Hepatol 2012)

- Recently updated data describing rates of major birth defects in newborns of women with in utero exposure to ARVs also approved for use in CHB infection
- Prospective enrollment, Jan 1989 – Feb 2011
  - 13,711 cases: only 2 drugs also used for CHB had sufficient exposure data (> 200 cases): LAM, TDF
- Birth defect prevalence with 1st Δ exposure to LAM or TDF similar to that for all ARV regimens (and comparable to background rate): 3.0% / 2.3% vs 3.0%
- For TDF, sufficient #s of 1st Δ exposures have been monitored to detect at least 2X increase in birth defects
  - For LAM, sufficient exposure data to detect 1.5X increase
  - To date, no such increases have been detected
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)
Is Testing and Treating for HBV Cost-Effective?

- Recent decision model analysis constructed for 2010 birth cohort of 4 million newborns
- Modeled to test 2 strategies, followed by maternal antiviral prophylaxis (lamivudine) from 28 weeks through 4 weeks postpartum
  - Testing was either HBeAg or HBV load ≥ 10^8 copies/mL
  - All newborns received active-passive immunoprophylaxis
- Both testing strategies produced savings, prevented chronic HBV infections, and saved QALYs
  - HBeAg was more cost-effective than load of 10^8 or 10^6
  - HBeAg has disadvantage of not being able to monitor response
- May have more application in resource-poor areas

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.