Introduction of Perinatal Transmission of Hepatitis B

Viral Hepatitis Prevention Board Meeting

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Perinatal Transmission - Epidemiology

- Global:
  - In 2015, WHO estimates that 257 million people are chronically infected with HBV, and 887,000 people died from complications of HBV-related liver disease.
    - Of the 257 million people infected, 9% (22 million) knew their diagnosis; treatment coverage was only 8% (1.7 million).
    - Mother-to-child transmission (MTCT) is responsible for more than one third of chronic HBV infections worldwide.

- United States:
  - In the United States, 850,000–2.2 million persons are estimated to be living with HBV infection.
  - Approximately 25,000 infants are born annually to hepatitis B infected pregnant women.

Natural History of Hepatitis B Virus (HBV) Infection

Transmission
• Perinatal
• Sexual
• Blood and Body fluids

Acute Hepatitis B

Asymptomatic or Symptomatic (including fulminant hepatitis)

Chronic Infection
- 90% of infants
- 30-50% of children <5 years
- 5-10% of adults
- Up to 50% in some chronic illnesses

Resolved & Immune

Liver failure, Death

Cirrhosis & Liver Cancer

Immunocompromised- Reactivation
Mother-to-child Transmission

- Approximately 90% of infants of HBsAg-positive/ HBeAg positive women and 5%–20% of infants of HBsAg-positive/ HBeAg-negative women become infected without intervention

- The most important risk factor for MTCT is the maternal HBV DNA level

- Most MTCT infant PEP failures occur at thresholds of maternal HBV DNA levels of $10^6$ to $10^8$ copies/mL


Pre-embryonic and Assisted Reproductive Therapy

- HBV has been detected in sperm, oocytes, and embryos

- Limited data suggest HBV transmission can occur in germline cells

- The risk of HBV transmission from persons with chronic HBV during assisted reproductive therapy is unknown; transmission possible

- Storage of cryopreserved sperm and embryos in the nitrogen vapor state, sperm washing, and double-sealing cryocontainers are suggested methods for reducing the possible risk of transmission
Prenatal

- The rate of intrauterine transmission is unknown but considered to be low

- The presence of maternal HBeAg (associated with higher HBV DNA levels) associated with prenatal transmission
  - HBeAg, only structural HBV protein that can pass through the placenta

- Transmission via amniocentesis has been reported at high HBV DNA levels
  - Not generally considered a risk factor
Intrapartum

- MTCT during delivery is most common
  - Exposure occurs through micro-transfusion or hematologic leaks of mother’s blood to the fetus during contractions, or through inoculation of mucosal membranes or breaks in the skin (e.g., scalp electrodes)
  - Most studies find no difference in MTCT among babies delivered by operative/spontaneous vaginal delivery or caesarean section when the infants receive PEP
  - Caesarian section is not recommended for reducing MTCT in the US
Breastfeeding

- Markers of HBV are detectable in breast milk and colostrum from HBsAg-positive women
- Reported rates of HBV-infection among breastfed and non-breastfed infants are similar, although some studies did not account for maternal HBV DNA levels
  - Considerations: cracked or bleeding nipples
Strategies for Prevention

- Maternal screening
- Hepatitis B (HepB) vaccination at birth (with passive immunoprophylaxis [HBIG]) and completion of HepB vaccine series
- Use of antivirals for high risk HBV-infected pregnant women
Maternal Screening

- Advisory Committee on Immunization Practices (ACIP) recommends screening pregnant women (including women previously vaccinated or previously tested) for HBsAg during the first prenatal visit of each pregnancy.

- Retest mother at or prior to delivery if HBsAg-negative earlier in pregnancy but presents for delivery with a risk factor identified:
  - >1 sex partner in previous 6 months
  - Evaluation or treatment for STD
  - Injection drug use
  - HBsAg-positive sex partner
  - Diagnosed with clinical hepatitis since last test

Pregnant Women Screening Algorithm

Screening and Referral Algorithm for Hepatitis B Virus (HBV) Infection among Pregnant Women

- **HBsAg**
  - Assess if at high risk for acquiring HBV infection
  - No further action needed
  - Consider vaccination during pregnancy or postpartum
  - Repeat HBsAg testing when admitted for delivery

- **HBsAg (positive)**
  - Report HBsAg positive pregnant women to Perinatal Hepatitis B Prevention Program
  - Identify all household and sexual contacts and recommend screening by primary care provider
  - Order Additional Tests:
    - HBeAg (hepatitis B e-antigen)
    - HBV DNA Concentration
    - ALT (alanine aminotransferase)

  - **HBsAg**
    - Refer for care postpartum
  - **HBsAg** or **HBV DNA >20,000 IU/mL** or **ALT >19 IU/L**
    - Refer to specialist immediately during pregnancy


U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

The American College of Obstetricians and Gynecologists

www.cdc.gov/hepatitis

March 2015
Identified U.S. births to Total Expected Births 2008-2014

- 2008-2014 Expected Birth Tables, DVH/NCHHSTP

![Graph showing Identified Births and Total Expected Births from 2008 to 2014.](2008-2014 Expected Birth Tables, DVH/NCHHSTP)
Post-exposure Prophylaxis (PEP)

- Prevention of MTCT by PEP, consisting of administering HBIG and a monovalent HepB vaccine within 12 hours of birth, followed by completion of the vaccine series, has 85%-95% efficacy

- HBIG (passive immunoprophylaxis) provides a short-term increase (i.e., 3-4 months) in anti-HBs which might improve protection until the infant responds to vaccine

- WHO recommends HBIG as an adjunct to HepB vaccine starting within 24 hours of birth, although the added benefit of HBIG is less clear among term infants of HBsAg-positive, HBeAg-negative women
  - Worldwide, administration of HBIG might not be feasible, because of supply, safety, or cost issues

- PEP success relies on timely completion of a 3-dose HepB vaccine series
Universal Birth Dose

- Global: WHO recommends the use of monovalent HBV vaccination within 24 hours of birth, regardless of HBsAg status of the mother, followed by completion of the HBV vaccine series within 6 to 12 months as the most cost-effective strategy for the prevention and control of hepatitis B

- United States: ACIP recommends birth dose within 12 hours for infants born to HBsAg positive mothers
  - 24 hours for all infants born to HBsAg-negative mothers (ACIP approved)
Birth Dose – Safety Net

The birth dose provides a “safety net” for
- Infants of HBsAg-positive women not identified for post-exposure prophylaxis (PEP) because of:
  - Medical errors in interpreting or documenting maternal screening results
  - Failure to test women at delivery who are admitted without prenatal HBsAg test results
- Infants who have contact with a HBsAg-positive caretaker or household member
- Infants at risk for exposure after the perinatal period

HBIG and Hepatitis B Vaccine Efficacy

- For prevention of MTCT of hepatitis B virus the efficacy* of
  - HBIG and HepB vaccine combined is ~94%
  - HBIG alone is ~71%
  - Hepatitis B vaccine alone is ~75%

*Based on infants of mothers HBsAg-positive and HBeAg-positive

- MTCT occurs in 5%-15% of infants despite timely prophylaxis


Hepatitis B Vaccine Coverage

- **Global**
  - In 2015, Birth dose coverage of hepatitis B vaccine, 39%
  - Three dose coverage of hepatitis B vaccine, 84%

- **United States**
  - In 2015, Birth dose coverage of hepatitis B vaccine, 72.4%
  - Three dose coverage of hepatitis B vaccine, 92.6%
Treatment During Pregnancy and Delivery

- The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level > 200,000 IU/mL

  - Quality/Certainty of Evidence: Low
  - Strength of Recommendation: Conditional

Clinical Trials

- Pan et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load
  - Enrolled 200 women with HBV DNA level >200,000 IU/mL
  - Non-breastfed infants received HBIg at birth and at week 4, and vaccine at birth, week 4 and week 24

- Jourdain et al. TDF To Prevent Perinatal Hepatitis B Virus Transmission: A Randomized Trial (iTAP)
  - Placebo-controlled, double-blind
  - Infants received hepatitis B vaccine (10 ug) at birth, 1, 2, 4 and 6 months, HBIg at birth

TDF Trial Conclusions (Pan et al.)

- At delivery, 68% of the mothers in the TDF group (66 of 97 women), as compared with 2% in the control group (2 of 100) had an HBV DNA level <200,000 IU/ml (P<0.001).

- At postpartum week 28, the rate of MTCT was significantly lower in the TDF group than in the control group
  - intention-to-treat analysis (transmission 5% of infants [5 of 97] vs. 18% [18 of 100], P = 0.007)
  - per-protocol analysis (transmission 0 vs. 7% [6 of 88], P = 0.01)

- The maternal and infant safety profiles were similar in the TDF group and the control group

TDF Trial Conclusions (iTAP)

- 331 women (168 TDF, 163 placebo) enrolled
  - HBV DNA load at enrollment: 8.0 log10 IU/mL (7.1, 8.5)
  - HBV DNA load at delivery: 3.9 log10 IU/mL (3.0, 4.8) on TDF, versus 7.8 log10 IU/mL (6.8, 8.5) on placebo

- 322 (97%) on-study deliveries (85 Cesarean, 26%)

- 323 live births
  - 320 (99%) infants received HBIg a median of 1.3 hours after birth
  - 322 (>99%) HB vaccine a median of 1.2 hours after birth

- In the primary complete case analysis at 6 months, 0/147 infants had HBV infection in the TDF arm versus 3/147 (2.0%) in the placebo arm (p=0.12)
- All 3 infected infants’ mothers had HBV DNA >7.8 log10 IU/mL at delivery

Elimination

- Perinatal transmission might be controlled or eliminated in regions with a combined strategy of:
  - Maternal screening,
  - Maternal antiviral treatment and
  - Infant post-exposure prophylaxis
References

References

References

For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.