Challenge of HBV prevention at pregnancy

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  – Bristol-Myers Squibb, Gilead Sciences, Bayer, Abbott and MSD
Prevalence of chronic HBV infection among pregnant women

Vertical transmission: Key factor of HBV infection in endemic area

In endemic area, Over 50% acquired their infection vertically from their mothers

> 90% become chronic HBV infection

Management of chronic HBV in pregnancy and strategies to prevent MTCT of HBV

240 million people with chronic HBV infection

Effects of pregnancy on chronic HBV infection

Normal pregnancy

↑Adrenal corticosteroids
Modulation of cytokines

Host immune response

Increase in HBV DNA levels but decrease in ALT

Hepatitis flares at late pregnancy or postpartum

Postpartum hepatitis flare in HBsAg-positive mothers

- Increased ALT within 6 months: 45%
- Overt liver dysfunction within 1 month in HBeAg-positive mothers (n=269): 43%
- HBeAg Seroconversion: 12-17%

The impact of maternal HBsAg carriers on pregnancy outcomes

- Threatened preterm labour at < 34 weeks: Maternal HBsAg carriers (11.9%) vs. Controls (6.3%, P = 0.030)
- Preterm labour at < 34 weeks: Maternal HBsAg carriers (4.7%) vs. Controls (1.2%, P = 0.033)
- Gestational DM: Maternal HBsAg carriers (19%), Controls (11.1%, P = 0.012)
- Antepartum hemorrhage: Maternal HBsAg carriers (11.5%) vs. Controls (5.5%, P = 0.026)
- Intraventricular hemorrhage: Maternal HBsAg carriers (4.7%) vs. Controls (0.8%, P = 0.007)

Multivariate analysis: threatened preterm labour, antepartum hemorrhage and gestational diabetes mellitus

Tse KY. et al. J Hepatol. 2005; 771-5
Mother to Child Transmission of HBV

- Intrauterine
- Intrapartum
- Postpartum

Intrauterine transmission of HBV

HBsAg or HBV DNA positive in neonatal blood within 24 h after births

- 3.7% in 402 HBsAg +ve mother
- 9.8% in HBeAg +ve mother

Risk factors for intrauterine HBV infection

- Maternal HBeAg positivity
- High maternal HBV DNA
- Threatened preterm labor
- Threatened abortion

Mother-to-Child Transmission of HBV is associated with high rate of progression to chronic HBV infection

Immunoprophylaxis for prevention of MTCT of HBV in infants born to HBeAg-positive Mothers

- No immunoprophylaxis: >90%
- HBIG within 12h of birth: 26%
- HBIG + HBV vaccine: 3% - 7%

Beasley RP. et al. Hepatology 1983; 3
Beasley RP. et al. Lancet 1983; 2
**Immunoprophylaxis to prevent MTCT of HBV: meta-analysis**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Relative Risk of neonatal HBV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV vaccine VS Placebo</td>
<td>0.28 (95% CI 0.2-0.4)</td>
</tr>
<tr>
<td>HBIG +HBV vaccine VS HBV vaccine</td>
<td>0.54 (95% CI, 0.41-0.73)</td>
</tr>
</tbody>
</table>

High maternal HBV DNA is associated with Immunoprophylaxis failure

<table>
<thead>
<tr>
<th>HBV DNA (log cp/ml)</th>
<th>Adjusted odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.9%</td>
<td>0.334</td>
</tr>
<tr>
<td>6</td>
<td>2.6%</td>
<td>0.165</td>
</tr>
<tr>
<td>7</td>
<td>6.6%</td>
<td>0.033</td>
</tr>
<tr>
<td>8</td>
<td>14.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>9</td>
<td>27.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• 10 of 303 babies born to HBV carrier mothers had HBV infection despite HBV vaccination
• All mothers of infected babies had positive HBeAg
• All infected babies had 3 doses of vaccine with HBIG at birth

Multivariate logistic regression model: Quantitative maternal HBsAg levels predicts immunoprophylaxis failure

All 162 infants with HBeAg-positive mothers and 331 of 364 (90.9%) with HBeAg-negative mothers received HBIG and HBV vaccination (9% of infants with HBeAg-ve mothers received only HBV vaccination)


Mother to Child Transmission of HBV

- 4 logs: 2.4%
- 4.5 logs: 8.6%
- 5 logs IU/ml: 26.4%

95% CI, 0.4-4.6 P=0.04
95% CI, 4.5-12.7 P=0.001
95% CI, 12.6-40.2 P<0.001
Antiviral therapy (Lamivudine or Telbivudine) can reduce maternal to child transmission of HBV

<table>
<thead>
<tr>
<th>Study name</th>
<th>RR (95% CI)</th>
<th>Events, Treatment</th>
<th>Events, Control</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBsAg seropositivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al. 2008</td>
<td>0.19 (0.07, 0.55)</td>
<td>4/70</td>
<td>12/40</td>
<td>24.08</td>
</tr>
<tr>
<td>Guo et al. 2011</td>
<td>0.34 (0.12, 0.93)</td>
<td>4/28</td>
<td>11/26</td>
<td>26.54</td>
</tr>
<tr>
<td>Li WF et al. 2006</td>
<td>0.17 (0.02, 1.35)</td>
<td>1/36</td>
<td>7/44</td>
<td>6.48</td>
</tr>
<tr>
<td>Xu et al. 2009</td>
<td>0.53 (0.14, 2.01)</td>
<td>3/56</td>
<td>6/59</td>
<td>15.22</td>
</tr>
<tr>
<td>Yang et al. 2008</td>
<td>0.95 (0.15, 6.08)</td>
<td>2/20</td>
<td>2/19</td>
<td>7.89</td>
</tr>
<tr>
<td>Yao et al. 2011</td>
<td>0.12 (0.01, 2.11)</td>
<td>0/28</td>
<td>4/30</td>
<td>3.28</td>
</tr>
<tr>
<td>Zhang and Wang. 2009</td>
<td>0.11 (0.01, 1.92)</td>
<td>0/31</td>
<td>4/30</td>
<td>3.28</td>
</tr>
<tr>
<td>Zhang et al. 2010</td>
<td>0.13 (0.02, 0.96)</td>
<td>1/50</td>
<td>8/50</td>
<td>6.53</td>
</tr>
<tr>
<td>Zhang et al. 2010</td>
<td></td>
<td>1/60</td>
<td>11/60</td>
<td>6.69</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p=0.639)</td>
<td>0.26 (0.16, 0.44)</td>
<td>16/379</td>
<td>65/358</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>HBV DNA seropositivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al. 2008</td>
<td>0.29 (0.12, 0.70)</td>
<td>6/70</td>
<td>12/40</td>
<td>25.87</td>
</tr>
<tr>
<td>Guo et al. 2011</td>
<td>0.19 (0.02, 1.49)</td>
<td>1/28</td>
<td>5/26</td>
<td>4.84</td>
</tr>
<tr>
<td>Xu et al. 2009</td>
<td>0.41 (0.22, 0.74)</td>
<td>11/56</td>
<td>27/56</td>
<td>59.11</td>
</tr>
<tr>
<td>Zhang et al. 2010</td>
<td>0.09 (0.01, 0.68)</td>
<td>1/60</td>
<td>11/60</td>
<td>5.15</td>
</tr>
<tr>
<td>Zhang et al. 2010</td>
<td>0.13 (0.02, 0.96)</td>
<td>1/50</td>
<td>8/50</td>
<td>5.02</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p=0.472)</td>
<td>0.31 (0.20, 0.49)</td>
<td>20/264</td>
<td>63/232</td>
<td>100.0</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Overall Rate Of Fetal Abnormalities

The rate of fetal abnormalities in the Telbivudine group (N=797) was 0.5, compared to 2.7 in the CDC General population.

Han GR, et al. Accepted at APASL 2013, Abstract # 388.
Rate of Hepatitis B Virus (HBV) Infection among Infants born to HBsAg positive mothers treated with TDF

Prospective randomized cohort HBeAg-positive mothers with HBV DNA > 200,000 IU/L

TDF was given from 30-32 weeks of gestation until postpartum week 4

Per-protocol analysis

Intention-to-treat analysis

Tenofovir Disoproxil Fumarate in HBeAg-positive mothers

HBeAg-positive mothers with HBV DNA > 7.5 log10 IU/ml

TDF was given from 30-32 weeks of gestation until 1 month postpartum based on their willingness.

No different rates of congenital anomaly, premature birth, growth parameters in infants and maternal creatinine.

Tenofovir to prevent perinatal transmission of hepatitis

Randomized 1:1 Double-blind placebo-controlled
HBeAg-positive Mothers
HBV DNA
ALT <30 IU/L at screening
28-week gestation

TDF 300 mg OD

Placebo

HBIG 10 μg at birth
HBV vaccine at birth at 1, 2, 4 and 6 months of age

28 week gestation to 2-months postpartum

HBV infection in infants at 6 months

The Hong Kong Association for the Study of Liver Diseases

The median time from birth to HBIG: 1.3 hours

The median time from birth to HBV vaccine: 1.2 hours


*: Analysis with missing data imputed as infected

P = 0.12

P = 0.60
### Guidelines for antiviral treatment in pregnant women with high viraemia

<table>
<thead>
<tr>
<th>EASL 2017</th>
<th>AASLD 2016</th>
<th>APASL 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all pregnant women with high HBV DNA levels ([200,000 \text{ IU/ml]}) or HBsAg levels ([4 \log_{10} \text{ IU/ml}]), antiviral prophylaxis with TDF should start at week 24–28 of gestation (Level 1, Grade 1).</td>
<td>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 (&gt;200,000 \text{ IU/ml}) (C1)</td>
<td>Short-term maternal NA starting from <strong>28 to 32 weeks</strong> of gestation is recommended using either tenofovir or telbivudine for those mothers with HBV DNA (&gt; 6 \log_{10} \text{ copies/ml}) (B2)</td>
</tr>
</tbody>
</table>

To stop or not to stop NA after delivery?
### Post-partum ALT flare

<table>
<thead>
<tr>
<th>ALT increase post-partum (ULN = 40 U/L)</th>
<th>TDF (N=97)</th>
<th>Control (N=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT 1.1–5x ULN</td>
<td>56%</td>
<td>32%</td>
<td>0.001</td>
</tr>
<tr>
<td>ALT 5.1–10x ULN</td>
<td>5%</td>
<td>6%</td>
<td>NS</td>
</tr>
<tr>
<td>ALT &gt;10x ULN</td>
<td>1%</td>
<td>3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

- **Any time during trial**: 62% vs. 41%, P = 0.004
- **Baseline to post-partum wk 4**: 16% vs. 22%, NS
- **Post-partum wk 5–28**: 46% vs. 30%, P = 0.03

Hepatitis flare after stopping NA

- Hepatitis flare may occur after stopping NA; can have ALT elevation to >5 x ULN

- 17% to 45% of women may experience a hepatitis flare (as compared to 25% in untreated CHB patients)

- Most hepatitis flares resolve spontaneously

- Hepatic decompensation rarely reported

### Safety of NUC in first trimester

<table>
<thead>
<tr>
<th></th>
<th>Nucleoside analogs</th>
<th>Nucleotide analogs</th>
<th>All antivirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth defects/non-live birth</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Spontaneous loss</td>
<td>0/287</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0/109</td>
<td>0/306</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>3/88</td>
<td>3.4</td>
<td>3/97</td>
</tr>
<tr>
<td>Induced abortions</td>
<td>7/353</td>
<td>2.0</td>
<td>7/395</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Overall</td>
<td>10/728</td>
<td>1.4</td>
<td>10/798</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

- No increase in birth defects
- No data on developmental delay and growth

## Guidelines for stopping antiviral treatment in pregnant women on antiviral treatment

<table>
<thead>
<tr>
<th>EASL 2017</th>
<th>AASLD 2016</th>
<th>APASL 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be continued up to 12 weeks after delivery (Level 1, Grade 1)</td>
<td>Antiviral therapy was discontinued at birth to 3 months postpartum in most of the studies. (C1)</td>
<td>The NAs could be stopped at birth and when breastfeeding starts, if there is no contraindication to stopping NAs (B2)</td>
</tr>
<tr>
<td></td>
<td>With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months. (C1)</td>
<td></td>
</tr>
</tbody>
</table>

Mode of delivery: MTCT of HBV

301 infants of HBsAg-positive mothers

HBsAg positivity %

- Vaginal delivery:
  - At birth: 8.1% (144), Chronic HBV infection: 7.3% (144)

- Vacuum or forceps:
  - At birth: 7.7% (40), Chronic HBV infection: 7.7% (40)

- Caesarian section:
  - At birth: 9.7% (117), Chronic HBV infection: 6.8% (117)

All infants received HBIG and vaccine

## Hepatitis B transmission by feeding and HBeAg status

<table>
<thead>
<tr>
<th>HBeAg</th>
<th>Breast-fed (n = 101)</th>
<th>Formula-fed (n = 268)</th>
<th>Total (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0/11</td>
<td>5/41</td>
<td>5/52 (9.6%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0/40</td>
<td>3/116</td>
<td>3/156* (1.9%)</td>
</tr>
<tr>
<td>Not done</td>
<td>0/50</td>
<td>1/111</td>
<td>1/161</td>
</tr>
<tr>
<td>Overall</td>
<td>0/101</td>
<td>9/268 (3.4%)*</td>
<td>9/369 (2.4%)</td>
</tr>
</tbody>
</table>

*P = .002 compared with HBeAg-positive women (Fisher exact test).
**P = 0.0639 compared with breast-fed

All infant received immuno prophylaxis with HB Ig and HBV vaccine at birth.

### Safety of breastfeeding in case of chronic hepatitis B virus infection of mothers

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of infants</th>
<th>Population</th>
<th>Prophylaxis</th>
<th>Infected or failed seroconversion to antiHBs</th>
<th>BF (%)</th>
<th>FF (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beasley et al</td>
<td>147</td>
<td>USA, Taiwan (China)</td>
<td>No</td>
<td></td>
<td>53</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Tseng et al</td>
<td>170</td>
<td>Hong Kong (China)</td>
<td>HBIG + Vx</td>
<td>7</td>
<td>6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>De Martino et al</td>
<td>85</td>
<td>Italy</td>
<td>Vx</td>
<td>4.6</td>
<td>3.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hill et al</td>
<td>369</td>
<td>USA</td>
<td>HBIG + Vx</td>
<td>0</td>
<td>3</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

BF: Breastfeeding; FF: Formula feeding; HBIG: Hepatitis B immune globulin; NS: Nonsignificant

Management of HBV during pregnancy

HBsAg+ve pregnant women

1st trimester check: LFTs, CBC, INR, HBeAg, HBeAb, HBV DNA levels

if active disease or advanced fibrosis: consider treatment with tenofovir or telbivudine

2nd trimester (at 24-28 weeks) check: ALT, HBV DNA levels

HBV DNA <200,000 IU/ml (10^6 copies/ml)
monitor

HBV DNA >200,000 IU/ml (10^6 copies/ml)
Consider treatment with tenofovir or telbivudine at 24-32 weeks

Stopping therapy at birth - 3 month post partum

HBIG and HBV vaccine given to newborn within 12 h. and complete 3-dose vaccination within 6 months

Breastfeeding

Postpartum monitoring for hepatitis flare in mothers

Piratvisuth T. Liver Inter. 2013

The Hong Kong Association for the Study of Liver Diseases
Thank you