Hepatitis B and Pregnancy

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Disclosure of Potential Conflicts of Interest

- Faculty: Carla S. Coffin

- Relationships with commercial interests:
  - Investigator Initiated Research Grant: GSK, Gilead Sciences
  - Educational Grants: Gilead Sciences
  - Advisory Board: Gilead Sciences, GSK
Learning Objectives: Hepatitis B and Pregnancy Update

• To explain issues regarding HBV epidemiology, prevention of mother to child transmission, and natural history in pregnancy

• To review evidence for initiating HBV therapy in pregnancy

• To review recommendations for monitoring and how to address post-partum HBV flares in treated and untreated patients

Specific Issues

• Prevention of Mother-to-Child-Transmission (MTCT)
  • 3-dose Infant Vaccine + Hepatitis B immune Globin
  • Tenofovir >Telbivudine >> Lamivudine - 28 weeks to 1-3 month post-partum if HBV DNA > 200,000 IU/mL

• Treatment of HBV during Pregnancy
  • Tenofovir if needed long term

• Effects of HBV Infection on Pregnancy
  • Limited Data -

• Effects of Pregnancy on the Course of HBV Infection
  • Limited Data; Monitor ALT q monthly - q 3 monthly
Prevalence of Hepatitis B Surface Antigen (HBsAg) Carrier State

Canada - ~2% prevalence. Higher risk immigrants, children of immigrants, dialysis, HCV or HIV+, street-connected
Vertical - Mother to Child during birth and Horizontal - close household contacts parent-child, child-child,

Schweitzer et al., Lancet 2015; Canadian Liver Foundation www.liver.ca

Risk of Chronic Hepatitis B Infection is Age dependent

• 80-90% of infants < 1 year
• 30-50% of children < 6 y
• <5% healthy adults (maybe even <1%)

WHO fact sheet July 2017

The WHO Recommends that all infants receive the HBV vaccine as soon as possible after birth, preferably within 24 hours
HBV Ig (HBIG) and Vaccine Dose Schedule in Babies of all HBsAg+ Positive Mothers

Vaccine ↓ ↓ ↓
HBIG ↓

<table>
<thead>
<tr>
<th>Birth</th>
<th>0</th>
<th>1</th>
<th>6</th>
</tr>
</thead>
</table>

Months of age
complete 3 dose vaccine and on schedule
If < 2000 g infant give 4-dose vaccine series

7-9 mo HBsAg and anti-HBs testing to confirm immunity

www.phac-aspc.ca.gc.ca, Canadian Immunization Guide

Impact of Universal HBV Vaccination in Infants on the Incidence Rate of Childhood HCC in Taiwanese Children, Adolescents and Young Adults

Impact of Universal HBV Vaccination in Infants on the Incidence Rate of Childhood HCC in Taiwanese Children, Adolescents and Young Adults

National Cancer Registry: 64 HCC cases in vaccinated* vs. 444 unvaccinated

* Incomplete vaccination and HBsAg+/HBeAg+ mothers

M-H Chang et al., J Natl Can Inst. 2009
Mother-to-Child Transmission: Significance of Viral Load

- 303 mother-infant pairs 10 CHB infants of HBeAg+ mothers (median DNA 8.4 log copies/mL) (Wen et al., J Hep 2013)

- **All had vaccine (by 1st week); HBIG to HBeAg(-) only unless self-paid.**

- **Risk:**
  - 2.5% 200,000 IU/mL (~6-log 10 copies)
  - 6.6% 2 million IU/ml (7-log_{10} copies)
  - 14.6% 20 million IU/ml (8-log_{10} copies)
  - 27.7% 200 million IU/ml (9-log copies)

* Wen W-H et al., J Hep 2013 V 59 24-30
Kubo Ann Intern Med 2014
Wiseman E, Med J Aust 2009
Zou H, JHV 2012

1 IU = 5.82 copies/ml

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Summary - HBV Oral Rx and Safety Data in Pregnancy

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>FDA Class</th>
<th>% Birth Defects T1 &amp; T2/T3</th>
<th>Pro/Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir</td>
<td>C</td>
<td>0 (N=48) &amp; 0 (N=0)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Entecavir</td>
<td>C</td>
<td>0 (N=58) &amp; 0 (N=2)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>C</td>
<td>3.1 (143/4566) 2.8 (204/7193)</td>
<td>++ human data, Not 1st line = resistance</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>B</td>
<td>0 (0/10) 0 (0/10) 2.3 (60/2608) 2.2 (24/1112)</td>
<td>+ human safety data (Less than LMV or TDF); Not 1st line = resistance</td>
</tr>
<tr>
<td>Tenofovir (TDF)*</td>
<td>B</td>
<td>Extensive human safety data</td>
<td></td>
</tr>
</tbody>
</table>

Class B - Animal studies show no risk to the fetus, Class C – Animal studies not conducted or show risk; consider risk vs. benefits; *Antiretroviral Pregnancy Registry International Interim Report 1989 2015; http://www.apregistry.com/forms/interim_report.pdf
1. Tenofovir – minimal active drug in breast milk and not absorbed via infant GI tract - TAF potential?
TDF to prevent Hepatitis B MTCT

200 Eligible Pregnant Women Randomized

100 control

12 withdrew

88 mothers / 88 infants

100 Tenofovir

6 withdrew/lost to follow-up
2 fetal/infant death

92 mothers / 92 infants

• TDF at 30-32 weeks until post-partum week 4
• All infants received immunoprophylaxis
TDF to prevent Hepatitis B MTCT

Pan et al., NEJM 374;24, June 16 2016

Quantitative Maternal Hepatitis B Surface Antigen Predicts Maternally Transmitted Hepatitis B Virus Infection

Bringing to an End Mother-to-Child Transmission of Hepatitis B: A Role for Quantitative Hepatitis B Surface Antigen?

G. Dusheiko

Wen et al., Hepatology 64, NO 5 2016
Quantitative maternal hepatitis B surface antigen predicts maternally transmitted hepatitis B virus infection

Estimated Rates of HBV Infection based on maternal qHBsAg levels

- Multiethnic cohort, 100 pregnancies
- Strong correlation between qHBsAg & HBV DNA in HBeAg+ patients (r = 0.79, P < 0.05),
- Optimal qHBsAg cut-off predicting maternal viraemia & risk immunoprophylaxis failure (i.e., HBV DNA ≥7 log IU/ml) is 4.3 IU/ml (accuracy 98.7%, 95% CI, 97–100%, P < 0.05)
- HBV DNA vs. qHBsAg costs $20K more per infection prevented.
Specific Issues

- Prevention of Mother-to-Child-Transmission (MTCT)
- Treatment of HBV during Pregnancy
- Effects of HBV on Pregnancy?
- Effects of Pregnancy on the Course of HBV Infection?
  - Cirrhosis is uncommon in young childbearing women
  - Due to delay in starting a family more women in the immune-active vs. immune tolerant (*high-replicative non-inflammatory*).
  - May already be on oral antiviral therapy → Switch to Tenofovir is preferred
  - Consider Pegylated-Interferon as first line due to finite duration if willing to delay starting a family.

Natural History: Limited Data

**Pregnancy**
- tolerance: increased adrenal corticosteroids, estrogens, progesterone
- *DNA Flares

**Cell Mediated Immunity**

**Post-Partum**
- Immune reconstitution
  - ALT Flares
  - HBeAg seroconversion

- Retrospective US study 1997-2015: 101 CHB untreated 9% HBV DNA flare; 6-10% asymptomatic ALT flare. 1 severe at 33 wks – C/S rescue Rx¹

- Pop’n based /case studies: HBV risk for adverse perinatal outcomes (preterm labour, induction, abruption PROM, gestational DM).²-³

Unanswered Questions

• Effects of TDF Exposure to the Infant?
  • Antiretroviral pregnancy registry - 1370 T1 exposures = no increase in birth defects
  • Affect bone density in babies born to HIV+ mother
  • New formulation (Tenofovir alafenamide) – less renal & bone toxicity?
  • Breastfeeding is “probably” safe - HIV+ cohort concentration <0.03% of recommended infant dose of TDF

Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region

- Prospective cohort study of 161 CHB pregnant mothers (most HBeAg -)
  - 23 treated HBV DNA > 7 log IU/ml
  - No adverse maternal/infant outcomes
- Mild maternal ALT flares—resolved
- No significant change in HBV DNA
- 98.8% of infants who completed HBIG+3-dose vaccine were immune
  - 1 infant born to an HBeAg+ mother with HBV-DNA >8-log IU/mL tested HBsAg+

G. Samadi-Kochaksaraei et al., JVH 2015

Peripartum cytokine flares in a multiethnic cohort of chronic hepatitis B carriers does not correlate with hepatitis B virus suppression or increased risk of liver disease

Shivani S. Joshi, Daniel Wong, Eliana Castillo, Mark G. Swain, Carla S. Coffin

<table>
<thead>
<tr>
<th>Pregnant type</th>
<th>TH1/TH2</th>
<th>TH1/TH2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFNγ/IL-4</td>
<td>IL-3/IL-5</td>
</tr>
<tr>
<td>Healthy (N=7)</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>CHB (N=38)</td>
<td>10</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Untreated HBV patients show increased Th1 cytokines in the peripartum period albeit with no significant change in viral load or ALT

Joshi S et al., Am. J. Reprod. Immun. 2017
**Summary: Management of HBV and Pregnancy (1)**

1. All pregnant women should be screened for HBsAg in the first trimester of pregnancy. (Strong recommendation, Class 1)
2. HBsAg positive pregnant women should undergo additional assessment with HBeAg, anti-HBe, HBV DNA and ALT and be referred to a specialist for management. (Strong recommendation, Class 1)
3. TDF is the drug of choice in pregnant women and women of childbearing potential who require immediate treatment of HBV. (Strong recommendation, Class 1)
4. Pregnant women with HBV DNA >200,000 IU/mL should initiate antiviral therapy at 24-32 weeks of gestation to reduce the risk of vertical transmission; TDF is the drug of choice and may be stopped at delivery or up to 12 weeks postpartum if given strictly to prevent MTCT. (Strong recommendation, Class 1)

*2018 CASL and AMMI HBV Management Guidelines, KE Doucette, Submitted*
Summary: Management of HBV and Pregnancy (2)

5. All women should be monitored for ALT flares post-partum with ALT every 4 weeks for the first 3 months, then at 6 months and followed by routine monitoring thereafter, (Moderate recommendation, Class 2 Level B)

6. All infants born to HBsAg positive mothers should receive immunoprophylaxis with HBIG and HBV vaccine within 12 hours of birth and completion of second and third HBV vaccine doses at 1 and 6 months respectively. (Strong recommendation, Class 1)

7. Babies should be tested with HBsAg and anti-HBs between 1 and 4 months after the last dose of vaccine to confirm they are uninfected and immune. (Strong recommendation, Class 2 Level A)

8. Breastfeeding is not contraindicated in either untreated HBsAg positive mothers or those on NA. (Strong recommendation, Class 1)

2018 CASL and AMMI HBV Management Guidelines, KE Doucette, Submitted
Acknowledgements

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• National Microbiology Laboratory: Dr. C. Osiowy,

• Alberta Provincial Laboratory: Kevin Fonseca, Carmen Charlton

• Funding Agencies

Thank you!
Tenofovir Alafenamide (TAF) Vemildy® (Gilead)

- Pro-drug of TDF (Viread®) in plasma metabolized inside cells to active form (25 mg po daily)
  - Lower serum bioavailability
    - Increased liver cell uptake
  - Less side effect TAF vs. TDF
    - Kidney: Cr increase 0.07 mg/dL vs 0.12 mg/dL (P = .02)
    - Bone Density: DEXA scan at baseline vs. Week 24, BMD loss of 0.8% vs 2.5% spine (P = .002) & 0.3% vs 2% in hip (P = .001)
  - No improved effect on Hepatitis B surface antigen
  - Long term data / post-marketing data needed

Summary:
In 4/21 CHB mothers variants at positions associated with classic VEM (i.e., G145R, P120S) was found at low frequency. B. Virine et al. PLOS One 2015

### Diagnostic Tests: Hepatitis B

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV Surface Antigen (HBsAg)</td>
<td>&gt; 6 months + = chronic infection</td>
</tr>
<tr>
<td>Quantitative HBsAg*</td>
<td>Treatment response, disease activity</td>
</tr>
<tr>
<td>HBV Surface antibody (anti-HBs)</td>
<td>- Response to the HBV vaccine</td>
</tr>
<tr>
<td></td>
<td>- If HBsAg loss and anti-HBs+ = Treatment response / host immune control (Yeah!)</td>
</tr>
<tr>
<td>HBV Core Antibody (anti-HBc)</td>
<td>Indicates exposure / any prior infection</td>
</tr>
<tr>
<td></td>
<td>Reactivation risk if immune-compromised / transplant? (Is there occult Hepatitis B?)</td>
</tr>
<tr>
<td>HBV E antigen</td>
<td>disease activity, infectivity, treatment response, “pre-core mutant”</td>
</tr>
<tr>
<td>HBV E antibody</td>
<td>disease activity, treatment response</td>
</tr>
<tr>
<td>HBV DNA (viral load)</td>
<td>disease activity, treatment response</td>
</tr>
<tr>
<td>HBV Genotype*</td>
<td>Response to Interferon / HCC risk</td>
</tr>
<tr>
<td>ALT</td>
<td>Hepatic inflammation / Liver Injury</td>
</tr>
<tr>
<td>FibroScan®/ Biopsy</td>
<td>Hepatic inflammation and fibrosis</td>
</tr>
</tbody>
</table>
Transmission of HBV

- Contact from blood or body fluids – not casual contact
  - 50 - 100 times more infectious than HIV
- Vertical
  - Mother-to-child during birth
- Horizontal
  - Close household contact / parent or child-to-child (early horizontal)
  - Blood-to-blood
  - Sexual contact

HBV Vaccine

- Recombinant hepatitis B surface antigen (HBsAg).
- Approved HBV vaccines:
  - ENGERIX®-B - GSK Inc., RECOMBIVAX HB® - Merck Inc., TWINRIX® – GSK
- 3 doses given 0, 1 and 6 months
- Robust, persistent HBV-targeted memory B & T cell responses in healthy individuals.
- Rare vaccine escape / failures (host HLA), immunosuppressed

Gilca et al., Hum Vaccine Immunother 2013; Gilca et al., Vaccine 2013; Carollo et al., Vaccine 2013; Beran et al., Vaccine 2016.

<table>
<thead>
<tr>
<th>Tested Prenatal Specimens (All Pregnancies)</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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<tr>
<td></td>
<td>53,590</td>
<td>57,002</td>
<td>59,339</td>
<td>59,675</td>
<td>59,206</td>
<td>58,932</td>
<td>60,166</td>
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</table>

<table>
<thead>
<tr>
<th>Number of Live Births</th>
<th>217</th>
<th>275</th>
<th>249</th>
<th>259</th>
<th>249</th>
<th>174</th>
<th>184</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBIG Given</td>
<td>216</td>
<td>275</td>
<td>248</td>
<td>258</td>
<td>245</td>
<td>173</td>
<td>183</td>
</tr>
<tr>
<td>HBV Dose 1</td>
<td>217</td>
<td>275</td>
<td>249</td>
<td>259</td>
<td>246</td>
<td>173</td>
<td>183</td>
</tr>
<tr>
<td>HBV Dose 2</td>
<td>214</td>
<td>273</td>
<td>244</td>
<td>252</td>
<td>240</td>
<td>164</td>
<td>104</td>
</tr>
<tr>
<td>HBV Dose 3</td>
<td>205</td>
<td>264</td>
<td>238</td>
<td>242</td>
<td>223</td>
<td>153</td>
<td>72*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology Results</th>
<th>171</th>
<th>232</th>
<th>196</th>
<th>204</th>
<th>178</th>
<th>109</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV Protected</td>
<td>171</td>
<td>227</td>
<td>196</td>
<td>203</td>
<td>177</td>
<td>109</td>
<td>16</td>
</tr>
<tr>
<td>HBV Infected</td>
<td>.</td>
<td>3</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Incomplete Testing to confirm protection (%)</td>
<td>(20)</td>
<td>(14)</td>
<td>(20)</td>
<td>(28)</td>
<td>(36)</td>
<td>(91)*</td>
<td></td>
</tr>
</tbody>
</table>

* Baby may not reached age to complete testing (i.e., at 7 – 9 months) or not yet reported; 3 failures – high HBV DNA

M. Osman personal communication Surveillance and Assessment Branch, Alberta Health and Wellness

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**AB Provincial Lab:**

Prenatal Report ~2011 onwards

- **Specimen:** Blood
- **Performed at:** ProvLab Calgary
- **Prenatal Delivery:** Not Provided
- **Hospital:**
- **Prenatal EDD:** Not Provided
- **Prenatal LMP:** Not Provided
- **Prenatal Hepatitis B & Surface Antigen:** Reactive

This pregnant patient has confirmed positive for Hepatitis B Surface Antigen on her prenatal screen. Expert management of HBV infection during pregnancy is a highly effective way of reducing mother to baby transmission of HBV. Please contact one of the two hepatitis clinics in Alberta for a priority consultation. In Calgary: Phone 403-210-9803 and Fax 403-210-7569 and in Edmonton: Phone 780-407-1650 and Fax 780-407-6659. Further, please ensure the availability of HBIG and the first dose of HBV vaccine at the delivery hospital for administration to the infant within the first few hours of birth. Public health follow-up will continue in the community and the remaining 2 doses of vaccine will be administered to the infant at the time of other routine immunisation. As this patient previously tested as confirmed positive for HBsAg, this specimen will not be reconfirmed.
Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis

• 26 studies, 10 RCT and 16 non-randomized = 3622 pregnant women (92% in China)
• Mother-Child Transmission (MTCT) defined as infant HBsAg positivity at 6 – 12 months
• Compared to control, Lamivudine and Telebivudine reduced MTCT (risk ratio 0.3, 95% CI 0.2-0.4) or infant HBV DNA seropositivity (risk ratio 0.3, 95% CI 0.2-0.5) (>70% reduction)
• Improved maternal HBV DNA suppression; no difference in PP hemorrhage, C/S.
• No difference in congenital malformations

Brown, RS Hepatology 2016;63:319-333