The Management of Hepatitis B During and After Pregnancy

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Potential Conflicts of Interest

- Consultant to Dynavax Technologies
Today’s Mission

- Chronic hepatitis B
  Natural history and treatment

- Mother to child transmission
  Global health perspective, mechanisms involved

- Antiviral therapy to further prevent MTCT
  Selection, safety, efficacy, management implications

- Breast feeding and anti-HBV therapy
  Safety, practice management
Hepatitis B

- 2 billion people in the world have been exposed
- 250 million people have chronic infection
  - ~2 million people in the USA
- Leading cause of primary liver cancer in the world
- Accounts for 600,000 deaths each year (half cancer, half liver failure-related)
Nomenclature for Today

HBsAg
Viral envelope protein; signifies ongoing infection

HBV DNA
Viral genome which is quantifiable in serum

HBeAg
Viral protein associated with high viral replication
(up to $10^{5-11}$ copies; copies divided by 5 = IU)

Anti-HBe
Appears after loss of HBeAg
Associated with non detectable or lower level of HBV DNA
($10^{4-8}$ copies) than HBeAg positive status
Hepatitis B Disease Progression

Acute Infection

Chronic Inflammation (HBeAg or anti-e positive)

Liver Cancer (HCC)

Cirrhosis

Liver Failure ( Decompensation)

Liver Transplantation

Death

30% lifetime

2-4%/yr

5-8%/yr

>90% of infected newborns

<5% of adults progress to chronic infection

~20% develop liver failure within 5 years of developing cirrhosis

vs
World Wide Prevalence of Chronic HBV Infection

HBsAg Prevalence
- High (>8%)
- Intermediate (2–8%)
- Low (<2%)

> 30% of chronic HBV infection is due to exposure at birth
60% of CHB in USA occurs in individuals born in intermediate or high risk regions

World Health Organization CDC Data
Maternal Transmission

- Transplacental (intrauterine)
  - No more than 5-10% of cases
  - Placental invasion by HBV or trafficking of infected PBMCs; HBV infection of spermatozoa or oocyte; amniocentesis-related

- Natal transmission (*perinatal, intrapartum*)
  - Accounts for majority of cases in world [risk increases with premature rupture of membranes]

- Post natal (breast feeding)
  - Reported to be rare
Efficacy of Immunoprophylaxis

- Maternal status HBeAg positive:
  - 90% of newborns infected
  - 90% of infected become chronically infected

- Maternal status HBeAg negative:
  - 5-15% of newborns infected

- Vaccine alone 85-90% efficacy; vaccine + HBIg: >90%
# Immunoprophylaxis Failure By Predelivery HBV DNA in 869 Infant-Mother Pairs

<table>
<thead>
<tr>
<th>Predelivery HBV DNA (copies/mL)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10^6 *</td>
<td>0</td>
</tr>
<tr>
<td>10^6-6.99</td>
<td>3.2</td>
</tr>
<tr>
<td>10^7-7.99</td>
<td>6.7</td>
</tr>
<tr>
<td>≥ 10^8</td>
<td>7.6</td>
</tr>
</tbody>
</table>

* 1 million copies equivalent to 200,000 IU

Zou et al, J Viral Hepat 2012; 19:e18-25
Many developing countries have not implemented effective programs

95% of new USA cases of chronic HBV infection are “imported” [Mitchell et al PLoS ONE 2011; 6:E277717]
- Major disparities in access to health care
- Estimated 65% of cases unaware

1,000 neonates infected annually in USA [IOM Report, 2010]

Failure to deliver birth dose or complete series occurs even in developed nations
Hepatitis B: Current Treatments in Adults

- Interferon alfa
- Lamivudine
- Adefovir
- Entecavir
- Telbivudine
- Tenofovir
  - Tenofovir alafenamide (safer, likely to be approved late 2016)
- Emtricitabine-tenofovir (for HIV coinfection, off label for HBV monoinfection)
## Oral Anti-HBV Agents and Pregnancy*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of FDA Approval</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg IFN alfa 2a</td>
<td>1992</td>
<td>Contraindicated during pregnancy [Category C with package warning]</td>
</tr>
<tr>
<td>Lamivudine (LVD)</td>
<td>1998</td>
<td>High rate of resistance. Category C for pregnancy</td>
</tr>
<tr>
<td>Adefovir</td>
<td>2002</td>
<td>Weak antiviral; no longer first line in US</td>
</tr>
<tr>
<td>Entecavir</td>
<td>2005</td>
<td>Resistance in &lt; 2% of patients at 8 years. No data during pregnancy. Category C</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>2006</td>
<td>Moderate rate of resistance; cross resistance with LVD. Category B</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>2008</td>
<td>No resistance at 8 yrs. Fanconi syndrome and bone demineralization. Category B</td>
</tr>
</tbody>
</table>

* None FDA approved during pregnancy
MTCT Rates in 686 Mother Infant Pairs

Zhang et al, Hepatology 2014; 60:648-76.
Telbivudine Safety During Pregnancy
(Piravisuth et al, World J Hepatol 2016 8:452-60)

• 1793 pregnancy outcomes (pooled data from clin. trials, used in combination with immunoprophylaxis)

• Prevalence of life birth defects (3.6/1000) no different with non antiviral maternal controls (3.0/1000)*

• Prevalence of spontaneous abortion (4.2/1000) no different from overall prevalence 16/1000*

• MTCT rate significantly lower (0.70% vs 11.9% non treated controls, p <0.0001)

* Compared to data from APR:www.APRegistry.com, through Jan, 2015)
Tenofovir Safety From Exposure Throughout Pregnancy

• Long term safety data incomplete
• USPHACS cohort (426 children) reports no impairment of fetal growth but possible delayed growth at 1 year [Siberry et al, *AIDS* 2012, 26:2119-20]
• Five studies with exposure throughout pregnancy show normal growth at birth and 12 months of age [Wang et al *HIV/AIDS* 2013; 1773-80]
## Liver Society Guidelines for Antiviral Therapy During Pregnancy

<table>
<thead>
<tr>
<th>Organization</th>
<th>When to treat</th>
<th>Which Agent to Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD (American)</td>
<td>Maternal HBV DNA level &gt;200,000 IU (1 million copies)</td>
<td>Lamivudine, telbivudine, or tenofovir with preference for tenofovir:&lt;br&gt;Breastfeeding not contraindicated</td>
</tr>
<tr>
<td>APASL (Asian)</td>
<td>HBV DNA level &gt;6 log IU (5 million copies)</td>
<td>Tenofovirus or telbivudine&lt;br&gt;Breastfeeding discouraged with antiviral</td>
</tr>
<tr>
<td>EASL (European)</td>
<td>HBV DNA level &gt;6 log IU</td>
<td>Lamivudine, telbivudine, or tenofovir&lt;br&gt;Breast feeding may not be considered a contraindication</td>
</tr>
</tbody>
</table>
A Hepatologist’s View of Hepatitis B Management During Pregnancy

HBsAg Positive

**ALT, HBV DNA testing**

- ALT normal, HBV DNA >2 x 10^5 IU
  - Antiviral started at week 28-30 until 1-3 mos post partum
  - Infant Receives HBIG + Vaccine at Birth
- ALT normal, HBV DNA <2 x 10^5 IU
- ALT abnormal, HBV DNA ≥ 10^4 IU
  - Non invasive imaging for fibrosis
  - Initiate antiviral as needed; continue post partum
Hepatitis Flares After Completion of Pregnancy

• Described in HBeAg positive and HBeAg negative HBsAg positive women:
  – Recovery of cellular immunity post partum in HBV DNA positive untreated mothers (*setting 1*, uncommon)
  – *Rapid resurgence* of HBV replication after treatment withdrawal with *immune rebound* (*setting 2*, more common, ~ 10-20 %)

• Requires follow up of mothers for at least 3 months (ALT surveillance with reflex HBV DNA testing)
Important Elements of Care

• Additional blood testing for HBV DNA needed to identify HBsAg-positive women with high viral level replication
• Maternal education about prevention should always but done and may prove vital in cultural acceptance of drug therapy
• Mothers treated in the last trimester have need for follow up after treatment withdrawal
Consultation Assistance

- Care of the pregnant HBsAg positive mother often facilitated by consultation with hepatologist or other health care provider skillful in the management of hepatitis B
Breast Feeding and Antiviral Therapy

• Breast feeding is acceptable for untreated HBsAg carriers but not when undergoing antiviral therapy

  – Small quantities of antiviral found in breast milk (2-4% of maternal plasma level)
  – Far more drug exposure to baby across the placenta
  – Parent drug >>active metabolite
  – Some risk that sudden withdrawal of antiviral therapy in highly replicative mothers can promote hepatitis flares

• Safety shown in newborns of HIV positive mothers treated with lamivudine or tenofovir throughout pregnancy (www.APRegistry.com)
Licensed Antivirals in the Pediatric Population

• **Interferon alpha-2b** (1 yr or older)
• **Lamivudine** (2 yrs or older)
• **Entecavir** (2 yrs or older)
• **Adefovir*** and **tenofovir** ** (12 yrs or older)
• **Telbivudine** (16 yrs or older)

* Shown to be no more effective than placebo in 2-11 yr olds
** Associated with rare renal dysfunction in adults and dec. bone mineral density in HIV infected children
Summary/Perspective

• MTCT occurs in 3-8% of properly immunized newborns

• Most of these cases can be prevented if highly viremic mothers are treated with antiviral Rx during the 3rd trimester
  Conservative (high viremia is > 200,000 IU = 1 million copies)
  More practical (high viremia is > 1 million IU = 5 million copies)

• Oral antivirals are safe for the mother and child during pregnancy

• Hepatologists abruptly terminate treatment at birth if mother is breast feeding. There are reasons to question this as a routine or standard of care measure.