HBV & HCV in pregnancy in the Jewish & Arab populations

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Liver Unit,
Hadassah Medical Center, Jerusalem

Viral Hepatitis Prevention Board Meeting

14-15/03/2013, Yad Hashmona Hotel, Jr
High global burden of chronic HBV & HCV infection

- HBV: 370 million
- HCV: 130 million
- HIV: 33 million
- HIV Co Infection: 6-9 million
- Total Viral etiologies: > 500 million
HCV infection is a major global health issue

- Major burden from sequelae of chronic infection:
  - 3-4 million newly infected each year,
  - 130-170 million chronically infected,
  - >350,000 deaths/year

- About 1% of pregnant women have HCV infection

- Corresponding to 40,000 births annually in the US
HCV vertical transmission rates varied between 2–6% in women without HIV


Belopolskaya Maria, 2012, Unpublished 2012
HCV Vertical transmission accounts for the vast majority of pediatric hepatic diseases

HCV = 43%

HBV = 25%

Belopolskaya Maria, 2012, Unpublished 2012

Risk factors of HCV vertical transmission
(No obstetric risk factors)

- **Mode of delivery**: There is no protective effect of cesarean delivery on HCV vertical transmission compared with vaginal delivery

- **Obstetric procedures**: prolonged rupture of membranes may increase risk, amniocentesis unlikely to increase risk

- **Prematurity**: No evidence of effect
Risk factors of vertical HCV transmission (viral risk factors)

- **HIV Co-infection**: increases vertical transmission risk 2–3-times, although this risk can be decreased with administration HAART during pregnancy

- **HCV viral load**: non-viraemic women have very low risk; high viral load increases vertical transmission risk

- **HCV-RNA in PBMCs** (peripheral blood mononuclear cells) increases risk of vertical transmission

Belopolskaya Maria, Russia, 2012, Unpublished 2012
A study was performed to determine the rate of HCV vertical transmission.

**Article**

Transient Transmission of Hepatitis C Virus from Mothers to Newborns

M. Ketzinel-Gilad, S.L. Colodner, R. Hadary, E. Granot, D. Shouval, E. Galun
**Methods:** 22 HCV+ mothers & their 23 newborns were monitored from early after birth *(No Arabs)*

<table>
<thead>
<tr>
<th>Mother no.</th>
<th>Age (years)</th>
<th>ALT (IU/l) (N:6–53)</th>
<th>Presumed route of HCV transmission</th>
<th>Liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>24</td>
<td>blood transfusion</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>152</td>
<td>not known</td>
<td>chronic hepatitis</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>63</td>
<td>blood transfusion</td>
<td>mild chronic hepatitis</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>93</td>
<td>blood transfusion</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>21</td>
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<td>6</td>
<td>41</td>
<td>27</td>
<td>health care work</td>
<td>ND</td>
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<tr>
<td>7</td>
<td>35</td>
<td>NA</td>
<td>not known</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>73</td>
<td>IVDU</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>44</td>
<td>not known</td>
<td>ND</td>
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<tr>
<td>10</td>
<td>23</td>
<td>48</td>
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<td>ND</td>
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<tr>
<td>11</td>
<td>27</td>
<td>117</td>
<td>blood transfusion</td>
<td>chronic hepatitis</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>57</td>
<td>health care work</td>
<td>ND</td>
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<tr>
<td>13</td>
<td>35</td>
<td>74</td>
<td>blood transfusion</td>
<td>chronic hepatitis</td>
</tr>
<tr>
<td>14</td>
<td>37</td>
<td>92</td>
<td>not known</td>
<td>chronic hepatitis</td>
</tr>
<tr>
<td>15</td>
<td>27</td>
<td>237</td>
<td>health care work</td>
<td>OLT with chronic hepatitis</td>
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<tr>
<td>16</td>
<td>37</td>
<td>133</td>
<td>blood transfusion</td>
<td>chronic hepatitis</td>
</tr>
<tr>
<td>17</td>
<td>35</td>
<td>91</td>
<td>not known</td>
<td>mild chronic hepatitis</td>
</tr>
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<td>18</td>
<td>40</td>
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<td>19</td>
<td>26</td>
<td>NA</td>
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<td>ND</td>
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<tr>
<td>20</td>
<td>36</td>
<td>98</td>
<td>spouse</td>
<td>ND</td>
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<td>21</td>
<td>23</td>
<td>77</td>
<td>blood transfusion</td>
<td>active cirrhosis</td>
</tr>
<tr>
<td>22</td>
<td>28</td>
<td>NA</td>
<td>blood transfusion</td>
<td>ND</td>
</tr>
</tbody>
</table>

NA, not available; ND, no diagnosis available; OLT, orthotopic liver transplantation.
Serological findings in the 22 HCV-infected mothers:

<table>
<thead>
<tr>
<th>Mother no.</th>
<th>Anti-HAV IgG</th>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>+</td>
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<td>4</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>22</td>
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</tr>
</tbody>
</table>

59% | 41%
HCV findings in 23 mother-newborn pairs: HCV antibodies & HCV-RNA

HCV-Ab’s were detected in the blood of all newborns immediately after birth

HCV-RNA was detected 2 days after birth in the blood of 5 infants (22%)

However, all dropped to low or undetectable levels by 7 months of age
Breastfeeding in HCV+ mothers

✓ Is considered safe unless nipples are cracked or bleeding

✓ Is not recommended if the mother is HIV positive

✓ HCV RNA can be detected in breast milk from women with high viral load (7% when HCV RNA>10(6)IU/ml)

Belopolskaya Maria, Russia, 2012, Unpublished 2012
HBV infection is a major global health issue

Major burden from sequelae of chronic infection:
Universal HBV vaccination for all newborns since 1992:

- Active for all neonates
- Passive if maternal HBsAg+
HBsAg should be screened in population at risk and according to an obvious indication.
Overview of Hepatitis B in Pregnancy

- Epidemiology
- Natural History and Outcomes in pregnancy
- HIV/HBV in Pregnancy
- Perinatal transmission

Israeli Data
The prevalence of HBsAg+ in Pregnancy

Low:
- US (<2%)
- African-American women - 1%
- Caucasian women - 0.6%
- Latina women - 0.14%

High:
- China: ~10%
- India: 1-9%
- Thailand 3-8%
- South Africa: 2-5%
- Cote D’Ivoire: 8%
- Uganda 5%
- Asian women - 6%

Sinha Hepatology Res 2010
<table>
<thead>
<tr>
<th>HBeAg (%)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2%</td>
<td>Ethiopia, Ghana, Nigeria</td>
</tr>
<tr>
<td>3.3%</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>4.6%</td>
<td>South Africa</td>
</tr>
<tr>
<td>9.5%</td>
<td>Senegal</td>
</tr>
<tr>
<td>16.1%</td>
<td>Zambia</td>
</tr>
<tr>
<td>24%</td>
<td>Southern Tanzania</td>
</tr>
</tbody>
</table>

Sinha Hepatology Research 2010
Outline

○ Overview of Hepatitis B in Pregnancy
    – Epidemiology
    – Natural History and Outcomes in pregnancy
    – HIV/HBV in Pregnancy
    – Perinatal transmission

○ Israeli Data
Impact of HBV on Pregnancy Outcomes

Yes: Association with:

✓ Increased gestational diabetes
✓ lower Apgar scores\textsuperscript{1,2}

No: No association with adverse pregnancy outcomes\textsuperscript{3-5}

1. Lao J Hepatol 2007
2. Tse J Hepatol 2005
3. Pastorek AJOG 1988
5. To Aust N Z J Obstet Gynaecol 2003
Impact of HBV on Pregnancy: Maternal Liver Disease

Liver disease:
- No liver disease worsening in majority of women\(^1\)
- Case reports\(^{2-4}\) of:
  - Hepatic exacerbations
  - Fulminant hepatic failures

Impact of Pregnancy on HBV

**HBV DNA levels**
- Overall increase in median HBV DNA levels during pregnancy (n=55)\(^1\)

- 4/16 (20%) HBeAg negative women had > 1 log increase in HBV DNA during pregnancy

- Even with lamivudine therapy
  - 7.8 log10 copies/mL \(\rightarrow\) 8.2 log10 copies/mL during pregnancy (P = 0.06), despite lamivudine therapy in 13 patients\(^2\)

1. Soderstrom SJID 2003
2. ter Borg JViralHep 2007
Outline

- Overview of Hepatitis B in Pregnancy
  - Epidemiology
  - Natural History and Outcomes in pregnancy
  - HIV/HBV in Pregnancy
  - Perinatal transmission

- Israeli Data
What is known about HIV & HBV in pregnancy?

✔ Prevalence
  - South Africa: 2.4%
  - Uganda: 4.9%
  - Zambia: 7.1%
  - Cote D’Ivoire: 9%

Barth Int J Infec Diseases 2010
HIV progresses HBV disease

✓ Higher HBV replication (HBV DNA & HBeAg+)\(^1\)

✓ Lower rate\(^4\) of
  - spontaneous loss of HBeAg
  - spontaneous loss of HBsAg
  - seroconversion to anti-HBe and anti-HBs

✓ Lower ALT levels\(^4\)

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Therefor, in HIV HBV co infection

- Higher rate of chronicity\(^2,3\)
  - 20 to 80% as compared to 3-5% in HIV -
  - increased risk with low CD4 at time of HBV acquisition

- Higher incidence of lamivudine resistance\(^4\)

- Faster progression to cirrhosis\(^4\)

- Higher mortality (compared to HIV or HBV mono infection)\(^2\)

Outline

- Overview of Hepatitis B in Pregnancy
  - Epidemiology
  - Natural History and Outcomes in pregnancy
  - HIV/HBV in Pregnancy
  - Perinatal transmission

- Israeli Data
When HBV Transmissions Happen?

✓ **In utero (<10%)**\(^1\): Associated with risk factors:
  - Acute HBV in third trimester
  - High Maternal Replication: HBeAg & high HBV DNA
  - History of threatened preterm labor
  - HBV in the placenta

✓ **At the time of delivery**\(^1\)
  - HBeAg-positive mothers: 85%
  - HBeAg-negative mothers: 31%

✓ **After birth**
  - Breastfeeding is not associated with transmission\(^2\)

---

2. Beasley Lancet 1975
HBV Transmission is Prevented by Postnatal Vaccination

<table>
<thead>
<tr>
<th></th>
<th>No Vaccine</th>
<th>Passive Immunization</th>
<th>Passive+Active Immunization are most effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants with HBV</td>
<td>95%</td>
<td>28%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Without immunoprophylaxis</th>
<th>HBIG &amp; HBV vaccine series</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>70-90%</td>
<td>5-10%</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>10-40%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Failures of Prophylaxis: Why?

✓ High maternal viral load

✓ Surface antigen mutations (e.g. G145R)

✓ Vaccine-related
  ▪ Poor quality assurance/storage
  ▪ Failure to complete schedule of vaccine
High maternal viral load

✓ Role of maternal HBV DNA on transmission\textsuperscript{1,2}:

\[ > \text{HBV DNA } 1.1 \times 10^7 \text{ IU/mL} = 32\% \text{ transmission} \]
\[ < \text{HBV DNA } 1.1 \times 10^7 \text{ IU/mL} = 0\% \text{ transmission} \]

✓ HIV/ HBV co infection had higher viremia\textsuperscript{3}

\textsuperscript{1.} del Canho R, et al. Vaccine. 1997;15:1624-1630
\textsuperscript{3.} Bodsworth NJ et al. J Infect Dis 1989
Prevention of HBV Transmission by maternal anti viral therapy
## Pregnancy Category of FDA-Approved Treatments for Chronic HBV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN alfa-2b</td>
<td>C</td>
</tr>
<tr>
<td>PegIFN alfa-2a</td>
<td>C</td>
</tr>
<tr>
<td>Adefovir</td>
<td>C</td>
</tr>
<tr>
<td>Entecavir</td>
<td>C</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>C</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>B</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>B</td>
</tr>
</tbody>
</table>

Drugs [package insert].
Lamivudine Treatment During Pregnancy

LAM given 1 month before delivery decreased HBV transmission:

- **from 28.0%** in untreated historical controls
- **to 12.5%** (OR: 2.9; 95% CI: 0.29-28.0)

- All received standard prophylaxis
- No adverse events noted with LAM

Telbivudine Treatment During Pregnancy

✓ **At birth:**
  – undetectable HBV DNA but HBsAg+ were 13(10%) Vs. 19(20%)
  – seropositive HBV DNA & HBsAg+ were 0 Vs. 9

✓ **At 7 month:**
  – seropositive HBV DNA & HBsAg+ were 0 Vs. 7
  – detectable anti-HBs
    
    132/132 (100%) Vs. 81/88 (92%) (t=10.845, P=0.001)

✓ The transmission rate were 0% (0/132) in telbivudine and 8% (7/88) in control group (t=10.845, P=0.001)

Tenofovir for prevention of HBV vertical transmission by highly viremic women

A retrospective study (2008-10) in 11 Asian HBV mono infected HBeAg+, pregnant women who received TDF in the third trimester.

A significant HBV-DNA reduction at delivery

All 11 infants received Active/Passive vaccination had no obstetric complication or birth defects.

All were HBsAg negative 28-36 wks after birth
Overview of Hepatitis B in Pregnancy

- Epidemiology
- Natural History and Outcomes in pregnancy
- HIV/HBV in Pregnancy
- Perinatal transmission

Israeli Data
Reported hepatitis B carriage rate in gravid women in Israel

- Is in the range of 0.6–4%
- With rates varying among ethnic groups

A population-based study in Negev women who delivered during the years 1988–2007, compared:

- HBsAg and/or anti-HCV seropositive women
- with all other pregnant women in the same period

Multivariable logistic regression models were constructed to control for confounders
749 hepatitis seropositive pregnant women were identified out of 186,619 deliveries (0.4%!!!).

Maternal characteristics, as well as perinatal outcomes, were comparable between the HBV and HCV carriers.
Comparison of characteristics between hepatitis carriers and non-carriers groups

Data are expressed as means ± standard deviation (SD), or numbers and percentages

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hepatitis carrier (n = 749) (%)</th>
<th>Comparison group (n = 185870) (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 18</td>
<td>0.7</td>
<td>1.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>19–35</td>
<td>80.0</td>
<td>86.2</td>
<td></td>
</tr>
<tr>
<td>36+</td>
<td>19.3</td>
<td>12.7</td>
<td></td>
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<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2500</td>
<td>10.4</td>
<td>7.8</td>
<td>0.029</td>
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<tr>
<td>2500–4000</td>
<td>84.5</td>
<td>87.3</td>
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<tr>
<td>&gt; 4000</td>
<td>5.1</td>
<td>4.8</td>
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<tr>
<td>Low birth weight (&lt; 2500 g)</td>
<td>11.2</td>
<td>19.3</td>
<td>0.06</td>
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<tr>
<td>Drug abuse</td>
<td>2.9</td>
<td>0</td>
<td>&lt; 0.001</td>
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<tr>
<td>Ethnicity</td>
<td></td>
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<tr>
<td>Jewish</td>
<td>81.7</td>
<td>54.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bedouin</td>
<td>18.3</td>
<td>45.9</td>
<td></td>
</tr>
<tr>
<td>Preterm delivery (&lt; 37 weeks)</td>
<td>9.9</td>
<td>16.9</td>
<td>0.08</td>
</tr>
</tbody>
</table>

The relative low rates of hepatitis carriers found in this study may represent an underdiagnosis in general and the Bedouins in particular.
Results:

HBV/HCV carriers had significantly higher rates of:

- Preterm deliveries (Po37 weeks gestation; 11.5 vs. 7.9%, Po0.001)
- Premature rupture of membranes (8.9 vs. 6.9%, P = 0.026)
- Placental abruption (1.5 vs. 0.7%, P = 0.018)
- Labor induction (33.9 vs. 28.1%, Po0.001)
- Caesarean deliveries (19.0 vs. 13.2%, Po0.001)
- Perinatal mortality (2.3 vs. 1.3%, P = 0.016)
- Congenital malformations (7.2 vs. 5.1%, P = 0.01)
- Cases with low birth weight (o2500 kg; 10.4 vs. 7.8%, P = 0.009)
Vertical HBV transmission in Jerusalem within the vaccine era

R Michael1,2, R Calderon Margalit2, E Shteyer3, Y Ashur4 & R Safadi1

1. Liver Unit, Institute of Gastroenterology and Liver Diseases, Division of Medicine. Hadassah- Hebrew University Medical Center, Jerusalem.
2. Braun School of Public Health and Community Medicine, Hebrew University-Hadassah, Jerusalem 91120, Israel.
3. Pediatric Gastroenterology Unit, Division of Pediatric, Hadassah-Hebrew University Medical Center, Jerusalem
4. Clalit Health Services, Jerusalem

Accounts ~77% of Arabic JR population

Safadi R, Harefua, 2013
A cross-sectional descriptive study was conducted in the year 2005-2006 at Clalit Health Services, Jerusalem.

Children at age ≥1 year born after 1992 for HBsAg positive mothers were evaluated.

**During the year 2005:**

20,415 members were screened for HBV:

- 55% (11,186/20,415) were Jewish.
- 45% (9,229/20,415) were Arab.

Safadi R, Harefua, 2013
HBsAg+ prevalence 2.64% among the general Jerusalem population (95% CI, 2.43-2.87)

- 3.9% among the Arabs (95% CI, 3.34-4.34);
- 1.59% (95% CI, 1.37-1.84) among the Jewish population.
HBsAg+ state in fertile women age 18-44 y

✓ 1.7% (total);
✓ 2.84% (95% CI, 2.43-3.3) in Arabs
✓ 0.66% (95% CI, 0.48-0.9) among Jewish women

Prevalence for 100

360

164 / 5778

2.84%

43 / 6461

0.66%

541

2.64%

Safadi R, Harefua, 2013
Of 164 Arab HBsAg+ fertile women, we identified 157 mothers for 409 children at age ≥1 year born after 1992

Data for 188 children to 70 mothers was collected:
- HBsAg
- HBc-Total Ab’S
- HBs-Ab’s

The prevalence of vertical infection among the children cohort

- Positive anti-HBc was 8.4% (95%CI, 4.71-13.1)
- positive HBsAg) was 4.4% (95%CI, 1.8-7.6)

Safadi R, Harefua, 2013
37.1% of these children had negative anti-HBs titters

✓ 41.4% with anti-HBs 11-100 mlU/ml
✓ 21.5% with titters above anti-HBs 100mlU/ml.

✓ 48% (23/48) children received passive-active vaccination
✓ 35% (17/48) children received only active vaccination

✓ 12.5% (6/48) were born to mothers prior to HBV infection diagnosis and received only the active vaccine.

✓ 4.5% (2/48) received no vaccination at all.

Safadi R, Harefua, 2013
Failures of Prophylaxis: Why?

- High maternal viral load

- Surface antigen mutations (e.g. G145R)

- Vaccine-related
  - Poor quality assurance/storage
  - Failure to complete schedule of vaccine
History of Hepatitis B Vaccines

Generations

1st
Plasma-derived
-HBsAg, Pre-S

2nd
Yeast-derived,
HBsAg

3rd
Mammalian cell d.
-HBsAg, Pre-S2
HBsAg, Pre-S2, Pre-S1

Sci-B-Vac

Eng. B
Summary
Proposed Recommendations for HBV-Infected Women Who Desire Pregnancy

✓ Women with mild liver disease, low viremia
  ▪ Pregnancy before treatment

✓ Women with moderate liver disease, no cirrhosis
  ▪ Treatment before pregnancy; if response, stop treatment before pregnancy

✓ Women with advanced liver disease
  ▪ Treatment before and during pregnancy; continue treatment after delivery

Women with mild liver disease, very high viremia

- Treatment in last trimester with “B” category drug with post-partum discontinuation

Thank You

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