Hepatitis C Virus Infection in Pregnancy

Mother to Infant Transmission

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Hepatitis C Virus

- Mainly parenteral transmission
  - Blood product transfusions prior to 1990, IVDU, tattoos

- As with HBV, liver injury immune-mediated

- 70% develop chronic liver disease (15% cirrhosis over 20 yr)

- Risk of hepatocellular carcinoma
  - Especially if cirrhosis
  - Incidence 1-6% annually
  - M>F (around 6:1)
Chronic Hepatitis C

• In the order of 0.2 - 0.5% of Australian population chronically infected

• Over 70% IV drug users infected

• Commonest indication for liver transplantation
HCV Infection in Pregnancy

Maternal Implications
I. General
II. Natural history in pregnancy and early post-partum

Neonatal Implications
I. Fetal outcome
II. Mother to infant transmission (MIT)
III. Natural history of MIT-acquired HCV infection
Maternal Implications

I. General –
Gestational Diabetes

• Increased incidence with maternal HCV infection
  – HCV-associated insulin resistance
Maternal Implications

I. General - Cholestasis of Pregnancy

- Increased incidence with maternal HCV infection
- Onset earlier in pregnancy
- Cholestasis of pregnancy in
  - 10/63 (5.9%) HCV +ve mothers
  - 135/16,208 (0.8%) HCV -ve mothers (P<0.001)
    » Locatelli et al, BJOG 1999;106:498-500

- Generally managed effectively with the bile acid, ursodeoxycholic acid
Maternal Implications

II. Natural History

• HCV RNA levels generally increase towards end of pregnancy
  – Reduced Th1-type cellular immunity
  – Expansion of CD4+, CD25+ Treg cells

• Liver enzyme levels generally improve (or even normalise) during 2nd and 3rd trimesters

• Disease flare may occur post-partum, with reconstitution of cellular immunity to pre-pregnancy state/surge in HCV-specific CD4+ and CD8+ responses
    – In concert with reduction in HCV load
    – 9% spontaneous resolution of viraemia
  • Hattori Y, et al. 2003;71:205-211
Maternal Implications

II. Natural History

• Nonetheless, anti-HCV immunity not completely suppressed in pregnancy.

• Both humoral and cell-mediated immune responses directed against HCV antigens occur throughout pregnancy
  - E2, p7, NS2, NS3, ARFP
    • Troesch M, et al. AIDS 2005;19:775-784

• Evolution of HCV quasispecies throughout pregnancy indicates on-going selective immune pressure on specific regions of E2
  - HVR1, HVR3
    • Troesch M, et al. Virology 2006;352:357-367
Infant Implications
I. Fetal Outcome

- Increased incidences
  - Premature rupture of membranes
  - Pre-term delivery
  - Placental abruption
  - Low birth weight
  - Congenital malformations
  - Overall perinatal mortality

- Other earlier, smaller studies showed no increased risk
Infant Implications

II. Mother to Infant Transmission

• Magnitude of Problem
  
  – 170 million worldwide chronically infected
  
  – If 35% are women of child-bearing age and annual fertility rate 2%

60,000 newborn babies will be infected with HCV each year
Infant Implications

II. Mother to Infant Transmission

- In utero or peri-partum?

- Infection early in utero accounts for at least some cases
  - Detection of HCV RNA in some infants as early as 24 hours after delivery
  - Presence of HCV variants in some infants that are not contemporaneous with maternal HCV quasispecies at birth

- Around one third of MIT instances may occur early in utero and one half late in utero/intra-partum

Infant Implications

II. Mother to Infant Transmission

• **Mechanism(s) of In Utero Transmission**

  – Via placenta, as amniotic fluid –ve for HCV RNA

  • Placental expression of several HCV receptors and entry co-factors on placenta (claudin-1, occludin, SR-B1, LDLr and DC-SIGN) supports hypothesis of direct infection, as recently shown *in vitro* using human cytотrophoblasts, leading to marked ultrastructural changes/reduced barrier function

  • Conversely, placental NK and NK T cells activated as a potential mechanism by which placenta may prevent MIT
Infant Implications

II. Mother to Infant Transmission - Risk Factors

• Maternal Viral Level

  – Most studies report instances of MIT only at HCV RNA levels $>6 \times 10^5$ copies/mL

• But broad overlap in levels of plasma HCV RNA above this threshold between transmitting and non-transmitting mothers

» Le Campion A, et al; Viruses 2012;4:3531-3550
Infant Implications

II. Mother to Infant Transmission – Risk Factors

• Rates among HCV RNA +ve / HIV -ve mothers (at around 36 months)
  – 5.6% (Italian)
  – 6.9% (Japanese) \( cf \) around 15% at birth
  – 3.1% (other)

• Rates among HCV RNA +ve / HIV +ve mothers
  – 3-4 fold increase
  – Co-infection increases the odds by 90%
    • Meta-analysis of 10 studies
Infant Implications

II. Mother to Infant Transmission – Risk Factors

• Mechanism(s) by which HIV co-infection enhances MIT rate of HCV unclear

  – Higher maternal HCV levels not consistently shown

  – ? HIV-induced immune suppression of HCV-specific immunity at materno-foetal interface

  – ? Impaired integrity of placental barrier due to HIV related chorio-amnionitis

  – ? HIV-facilitated HCV entry and replication in PBMC’s
    » Blackard JT. J Infect Dis 2005;192:258-265
Infant Implications

II. Maternal to Infant Transmission – Risk Factors

- MIT may be related to maternal PBMC infection with HCV
  - +ve strand HCV RNA found in PBMC’s of 13/13 mothers who transmitted infection cf 13/53 of mothers who did not (P<0.0001)
  - -ve strand HCV RNA found in PBMC’s of 5/13 and 0/53 cases, respectively (P<0.001)

Infant Implications

II. Mother to Infant Transmission – Lack of Available Preventative Strategies

• Unlike in HBV setting, pharmacological prevention of MIT not possible currently
  – Pegylated IFN and ribavirin contraindicated in pregnancy
    • A number of directly-acting anti-viral drugs becoming available in the non-pregnancy setting (boceprevir, telaprevir, etc)

• Similarly, no immunoglobulin or vaccine available for baby from birth
Infant Implications

II. Mother to Infant Transmission - Risk Factors

- Amniocentesis

<table>
<thead>
<tr>
<th>Studies identified</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. subjects</strong></td>
<td></td>
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<tr>
<td>Amniocentesis</td>
<td></td>
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<tr>
<td>1 cohort study *</td>
<td>cohort study of second trimester amniocentesis showed no instances of MIT in the 10 babies tested</td>
</tr>
<tr>
<td>n=10</td>
<td></td>
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<tr>
<td>1 case report **</td>
<td>case of MIT following second trimester amniocentesis, but potential confounding factors could not be excluded</td>
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** Minola E, et al. Hepatology 2001;33:1341-1342
## Infant Implications

### II. Mother to Infant Transmission - Risk Factors

- **Labour Management**

<table>
<thead>
<tr>
<th>Studies identified* No. subjects</th>
<th>Summary</th>
</tr>
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<tbody>
<tr>
<td><strong>Internal foetal monitoring</strong>&lt;br&gt;versus&lt;br&gt;Not</td>
<td>3 cohort studies n=928</td>
</tr>
<tr>
<td><strong>Prolonged membrane rupture (&gt;6 hours)</strong>&lt;br&gt;versus&lt;br&gt;<strong>Shorter duration</strong></td>
<td>2 cohort studies n=245</td>
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</tbody>
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* to May 2012

### Infant Implications

**II. Mother to Infant Transmission - Risk Factors**

- **Mode of Delivery**

<table>
<thead>
<tr>
<th>Studies identified* No. subjects</th>
<th>Summary</th>
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<tbody>
<tr>
<td>Elective caesarean versus Vaginal delivery</td>
<td>4 cohort studies n=2080</td>
</tr>
<tr>
<td>Any caesarean versus Vaginal delivery</td>
<td>11 cohort studies n=2308</td>
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</tbody>
</table>

* to May 2012  
## Infant Implications

### II. Mother to Infant Transmission - Risk Factors

- **Breast Feeding**

<table>
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<tr>
<th>Studies identified* No. subjects</th>
<th>Summary</th>
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<tr>
<td>Breast feeding versus No breast feeding</td>
<td>14 cohort studies n=2971</td>
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</table>

* to May 2012

Infant Implications

III. Natural History of HCV Infection Acquired by MIT

• Spontaneous clearance influenced by non-genotype 1 and IL28B genotype
  – Chronic infection rate 17% for CC genotype, 78% for non-CC genotype

• As in adults, most chronically-infected children are asymptomatic
  – Natural history similar to that when infection is acquired in adulthood (indolent in most)
  – Trials of directly-acting anti-viral drugs underway

• Report of a child with MIT-acquired HCV with high levels of circulating HCV RNA despite remaining sero-negative up to 10 years of age
  – Analogous to vertically-acquired HBV infection: neonatal tolerance/long-term sero-negativity/chronic viral persistence