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

» Pergam SA, et al. Am J Obstet Gynecol 2008;199:38
» Buresi MC, et al. J Obstet Gynaecol Can 2010;32:935-941
» Reddick KL, et al. J Viral hepat 2011;18:e394-e398

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
    - » Paternoster et al, Acta Obstet Gynecol Scand 2002;81:99-103
  - 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***
    - *Watanable M, et al. Am J Reprod Immuniol 1997;37:368-377*
  - ***Expansion of CD4+, CD25+ Treg cells***
    - *Aluvihare VR, et al. Nat Immunol 2004;5:266-271*

- **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**
  - Honegger J, et al. Proc 47th Annual Meeting Inf Dis Soc Am, 2009
  - ***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

Imfant Implications
I. Fetal Outcome

- Increased incidences
  - Premature rupture of membranes
  - Pre-term delivery
  - Placental abruption
  - Low birth weight
  - Congenital malformations
  - Overall perinatal mortality
    - » Safir A, et al. Liver Int 2010;30:765-770
    - » Connell LE, et al. Liver Int 2011;DOI:1111/j.1478-3231.2011.02556.x
- Other earlier, smaller studies showed no increased risk
  - » Floreani A, et al. BJOG 1996;103:325-329
  - » Jabeen T, et al. QJM 2000;93:597-601

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***
    - » **Resti M, et al. BMJ 1998;317:437-441**
    - » **Pollack H, et al. J Acquir Immune Defic Synd 2004;36:890-899**
    - » **Le Campion A, et al. Viruses 2012;4:3531-3550**

Infant Implications

II. Mother to Infant Transmission

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

  - **Via placenta, as amniotic fluid –ve for HCV RNA**
    - » **Delamare C, et al. 1999;31:416-420**

    - **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 cytotrophoblasts, leading to marked ultrastructural changes/reduced barrier function**
      - » **Dye JF, et al. Placenta 2001;22:32-43**
      - » **Ethier-Chiasson M, et al. Biochem Biophys Res Comm 2007;359:8-14**
      - » **Soilleux EJ, et al. J Immunol 2000;165:2937-2942**
      - » **Nie QH, et al. J Med Virol 2012;84:1586-1592**

    - **Conversely, placental NK and NK T cells activated as a potential mechanism by which placenta may prevent MIT**
      - » **Waasdorp Hurtado CW, et al. PLoS One 2010;5:e12232**

Infant Implications
II. Mother to Infant Transmission - Risk Factors

- **Maternal Viral Level**
  - **Most studies report instances of MIT only at HCV RNA levels >6 X 10^5 copies/mL**
    - **But broad overlap in levels of plasma HCV RNA above this threshold between transmitting and non-transmitting mothers**
      - » **Indolfi G, et al. J Med Virol 2009;81:836-843**
      - » **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
      - » Papaevangelou V, et al. J Infect Dis 1998;178;1047-1052

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**
    - » **Zanetti AR, et al. Lancet 1995;345:289-291**
    - » **Conte D, et al. Hepatology 2000;31:751-755**
  - **? HIV-induced immune suppression of HCV-specific immunity at materno-foetal interface**
  - **? Impaired integrity of placental barrier due to HIV related chorio-amnionitis**
    - » **Kwiek JJ, et al. PLoSMed 2006;3:e10**
  - **?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)**
    - » **Azzari C, et al. Blood 2000;96:2045-2048**

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**

	Studies identified No. subjects	Summary
Amniocentesis	1 cohort study * n=10	Cohort study of second trimester amniocentesis showed no instances of MIT in the 10 babies tested
	1 case report **	Case of MIT following second trimester amniocentesis, but potential confounding factors could not be excluded

*** Delamare C, et al. J Hepatol 1999;31:416-420**
**** Minola E, et al. Hepatology 2001;33:1341-1342**

Infant Implications

II. Mother to Infant Transmission - Risk Factors

- **Labour Management**

	Studies identified* No. subjects	**Summary**
Internal foetal monitoring versus Not	3 cohort studies n=928	Three studies (two good quality) report inconsistent results – no significant difference in two and increased risk of MIT in one of the good quality studies (adjusted OR 6.7, 95% CI 1.1-36)
Prolonged membrane rupture (>6 hours) versus Shorter duration	2 cohort studies n=245	Both studies (one good quality, the other poor quality) found association between longer duration of rupture of membranes and risk of MIT (adjusted OR 9.3, 95% CI 1.5-180 in the good quality study)

*** to May 2012**

Cottrell EB, et al. Ann Intern Med 2013;158:109-113

Infant Implications
II. Mother to Infant Transmission - Risk Factors

- **Mode of Delivery**

	Studies identified* No. subjects	**Summary**
Elective caesarean versus Vaginal delivery	4 cohort studies n=2080	The two good quality studies found no statistically significant difference in MIT rates
Any caesarean versus Vaginal delivery	11 cohort studies n=2308	10/11 studies (one good quality) found no statistically significant difference in MIT rates

*** to May 2012**

Cottrell EB, et al. Ann Intern Med 2013;158:109-113

Infant Implications
II. Mother to Infant Transmission - Risk Factors

- **Breast Feeding**

	Studies identified* No. subjects	**Summary**
Breast feeding versus No breast feeding	14 cohort studies n=2971	All 14 studies found no significant association between breast feeding and risk of MIT

*** to May 2012**

Cottrell EB, et al. Ann Intern Med 2013;158:109-113

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
    - » Ruiz-Extremera A, et al. Hepatology 2011;53:1830-1838
- 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
    - » Larouche A, et al. J Clin Microbiol 2012;50:2515-2519