Clinical Management of Viral Hepatitis During Pregnancy and Breastfeeding

Roma, 23 Febbraio 2011

13th Pre-Meeting Course
Difficult Clinical Issue in Hepatology

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Associazione Italiana per lo Studio del Fegato
# Epidemiological Profile of Italian Children with Hepatitis C

**Italian Observatory for Hepatitis C in Children**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>transfusions</td>
<td>200 (55%)</td>
<td>17 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>other parenteral exposure</td>
<td>40 (11%)</td>
<td>10 (5%)</td>
<td>3 (1.5%)</td>
<td>0</td>
</tr>
<tr>
<td>infected mother</td>
<td>82 (22%)</td>
<td>123 (66%)</td>
<td>152 (84%)</td>
<td>52 (93%)</td>
</tr>
<tr>
<td>infected family contact</td>
<td>7 (2%)</td>
<td>3 (1%)</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>unknown</td>
<td>26 (10%)</td>
<td>24 (18%)</td>
<td>20 (14%)</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

*Bortolotti et al. J Hepatol 2007;46:783-90*
PRECONCEPTION CARE
Mother to Child Transmission of Hepatitis C Virus from HIV Seronegative Women

Tuscany Study Group on Hepatitis C Virus Infection

mother-infant pairs:  25,654

HCV-infected mothers:  442 (1.7%)

HCV viraemic mothers:  275 (68%)
Epidemiology of Mother to Child Transmission

Weighted Rate of Perinatal Transmission of HCV

- **1.7%** when the mother was anti-HCV positive irrespective of HCV RNA
- **4.3%** when the mother was positive for HCV RNA
- **19.4%** when the mother was coinfected with HCV and human immunodeficiency virus

Maternal HCV Viraemia

Tuscany Study Group on Hepatitis C Virus Infection

- transmission from HVC-viraemic mothers: 5% (13/257)
- transmission from HVC RNA negative mothers: 0

- perinatal transmission is almost always confined to women with HCV viremia

Level of Maternal HCV Viraemia

Conflicting Results

- some studies reported that a high concentration of serum HCV RNA is associated with a higher risk of transmission

  Ceci et al. J Pediatr Gastroenterol Nutr 2001;33:570–75
  Okamoto et al. J Infect Dis 2000;182:1511–4

- considerable overlapping in concentrations of HCV RNA between transmitting and non-transmitting mothers

HCV Infection in Pregnancy

Viraemia and Transaminases

Gervais et al. J Hepatol 2000;32:293-9
**HCV Infection in Pregnancy**

**Viraemia**

- Serum HCV RNA (copies × 10⁶/mL)

<table>
<thead>
<tr>
<th>Time of Determination</th>
<th>Number of Tested Subjects</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td>65</td>
<td>12.0</td>
<td>19.9</td>
</tr>
<tr>
<td>Second trimester</td>
<td>64</td>
<td>10.9</td>
<td>13.3</td>
</tr>
<tr>
<td>Third trimester</td>
<td>64</td>
<td>19.5</td>
<td>25.1</td>
</tr>
<tr>
<td>6 mo after delivery</td>
<td>60</td>
<td>9.2</td>
<td>19.0</td>
</tr>
</tbody>
</table>

Paternoster et al. Am J Gastroenterol 2001;96:2751-4
**HCV Infection in Pregnancy**

**Transaminases**

- AST and ALT (data are median values)

<table>
<thead>
<tr>
<th>Time of Determination</th>
<th>AST U/L</th>
<th>Range</th>
<th>ALT U/L</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td>27</td>
<td>17–115</td>
<td>47</td>
<td>12–172</td>
</tr>
<tr>
<td>Second trimester</td>
<td>26</td>
<td>12–86</td>
<td>26*</td>
<td>8–80</td>
</tr>
<tr>
<td>Third trimester</td>
<td>28</td>
<td>13–117</td>
<td>22*</td>
<td>8–166</td>
</tr>
<tr>
<td>6 mo after delivery</td>
<td>38</td>
<td>15–168</td>
<td>54</td>
<td>9–137</td>
</tr>
</tbody>
</table>

*Paternoster et al. Am J Gastroenterol 2001;96:2751-4*
Viral Factors

HCV Genotype

- no correlation between perinatal transmission of HCV and maternal HCV genotype has been demonstrated

Zanetti et al. J Hepatol 1999;31:96–100
**Mother to Child Transmission of HCV**

**HIV Coinfection**

- maternal HCV-HIV coinfection is associated with an increased risk of perinatal transmission of HCV

**References**

Mother-to-infant transmission of multiple blood-borne viral infections from multi-infected mothers.

<table>
<thead>
<tr>
<th>Viral associations in the mothers</th>
<th>n (%)</th>
<th>Viral associations in the infants (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 HCV TTV HGV</td>
<td>4 (6.25)</td>
<td>HGV (1)</td>
</tr>
</tbody>
</table>
| HIV-1 HCV TTV                    | 12 (18.75) | **HIV-1 – TTV (1)**  
**HIV-1 (2), HCV (1), TTV (2)** |
| HIV-1 HCV HGV                    | 4 (6.25) | HIV-1 (1), HGV (1) |
| HIV-1 HCV                        | 13 (20.31) | HCV (1) |
| HCV TTV                          | 5 (7.81) | **HCV – TTV (2)**  
TTV (1), HCV (1) |
| HCV HGV                          | 3 (4.69) | **HCV – HGV (1)**  
HGV (1) |
Several but not all studies have shown that the maternal history of intravenous drug use involves a greater risk for perinatal transmission of HCV

Resti et al. J Infect Dis 2002;185:567–72
Zanetti et al. Intervirology 1998;41:208–2
Mother to Child Transmission of HCV

Alanine Transaminase Concentration

- abnormal alanine transaminase concentration during the last year before pregnancy and at delivery in mothers infected with HCV is associated significantly with perinatal transmission of HCV

HCV infection of the fathers, who were also the sexual partners of the HCV-infected mothers, was predictive of HCV perinatal transmission.
MOTHER TO CHILD TRANSMISSION OF HCV

- VIRAEMIA
- INTRAVENOUS DRUG USE
- HIV-HCV COINFECTION
- INCREASED ALT BEFORE PREGNANCY
- HCV INFECTION OF THE FATHER
MOTHER TO CHILD TRANSMISSION OF HCV

- Viraeemia
- Increased ALT before pregnancy
- Intravenous drug use
- HIV-HCV coinfection
- HCV infection of the father
Mother to Child Transmission of HCV

PBMNC Infection

- HCV RNA in maternal PBMNC is highly associated with transmission of HCV to the newborn.

- The presence of negative-strand HCV RNA (a marker of HCV replication in maternal PBMNC) is associated with mother to child transmission.


- 158 mothers: HIV-1-HCV coinfected
- 739 mothers: HCV monoinfection

- intravenous drug use
- HIV-1 coinfection

increase the risk of mother to child transmission

158 mothers
HIV-1-HCV coinfection

739 mothers
with HCV monoinfection

intravenous drug use

HIV-1 coinfection

increases the risk of mother to child transmission

multivariate analysis

51 HCV-positive women with a previous history of intravenous drug use

57 HCV-positive women

Previous history of intravenous drug use increases the risk of PBMNC infection by HCV
Higher risk of hepatitis C virus perinatal transmission from drug user mothers is mediated by peripheral blood mononuclear cell infection.


- 48 HCV transmitting mothers
- 122 non-transmitting mothers

PBMNC infection

Increases the risk of mother to child transmission

Intravenous drug use

- 48 HCV transmitting mothers
- 122 non-transmitting mothers

PBMNC infection increases the risk of mother to child transmission. Intravenous drug use is not associated with transmission.

Multivariate analysis

49 HCV transmitting mothers

557 non-transmitting mothers

intravenous drug use

increases the risk of mother to child transmission

HCV infection of the father
Intrafamilial transmission of hepatitis C virus.

**Cases**
- 49 HCV transmitting mothers

**Controls**
- 557 non-transmitting mothers

- Intravenous drug use increases the risk of mother to child transmission
- Multivariate analysis
MOTHER TO CHILD TRANSMISSION OF HCV

VIRAEMIA

PBMC INFECTION

INCREASED ALT BEFORE PREGNANCY

INTRAVENTOUS DRUG USE

HIV-HCV COINFECTION

HCV INFECTION OF THE FATHER
MOTHER TO CHILD TRANSMISSION OF HCV

- VIRAEemia
- PBMC INFECTION
- INCREASED ALT BEFORE PREGNANCY
- INTRAVENOUS DRUG USE
- HIV-HCV COINFECTION
- HCV INFECTION OF THE FATHER
PREGNANCY, DELIVERY and BREASTFEEDING
In amniocentesis, a hollow needle is inserted through the mother's abdomen into the uterus, and amniotic fluid is drawn for analysis.
Obstetric Procedures and Intrapartum Exposure to Maternal Blood Infected by HCV

Amniocentesis

- HCV was found in amniotic fluid in only 6.3% of HCV viremic mothers who underwent amniocentesis during the fourth month of pregnancy


- one study demonstrated that amniocentesis is a potential risk for spreading HCV infection to the infant

Minola et al. Hepatology 2001;33:1341–2
Exposing the Infant to Maternal Blood

Obstetric Procedures and Intrapartum Exposure to Maternal Blood Infected by HCV

- **invasive monitoring** of the fetus in labor with a scalp, vaginal or perineal laceration during vaginal delivery increase the risk of perinatal transmission of HCV

  *Mast et al. J Infect Dis 2005;192:1880–9*
  *Steininger et al. J Infect Dis 2003;187:345–35*

- in twin pregnancies the transmission of HCV is more likely to affect the second twin

Prolonged Rupture of Membrane and Delivery Complications

Conflicting Results

- membrane rupture occurring more than 6 hr before delivery is associated with an increased risk of perinatal transmission of HCV

European Paediatric Hepatitis C Virus Network J Infect Dis 2005;192:1872–9

- one study failed to demonstrate this association

Factors Not Associated with Mother to Child Transmission

Mode of Delivery

- the mode of delivery (Caesarean section versus vaginal route) does not affect the risk of perinatal transmission of HCV

Ceci et al. J Pediatr Gastroenterol Nutr 2001;33:570–75
Resti et al. J Infect Dis 2002;185:567–72
Mode of Delivery

Elective Caesarian Section

- delivery by elective Caesarean section before membrane rupture was associated with a lower risk of transmission than with delivery by vaginal route or by emergency Caesarean section

Currently, there is no evidence from randomised controlled trials upon which to base any practice recommendations regarding planned caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission.

No good evidence to support using caesarean section for reducing mother to baby transmission of hepatitis C during labour and birth.

Cochrane Database Syst Rev 2006;4:CD005546
Subsequent Delivery of a Child Infected Perinatally with HCV

Recurrence Risk

- only one study evaluated the risk of recurrent perinatal transmission of HCV in offspring in subsequent pregnancies. The risk does not seem to increase in consecutive siblings of the same infected mother

Factors Not Associated with Mother to Child Transmission

Mother–Child Human Leukocyte Antigen Concordance

- mother–child HLA class-1 type discordance, previously shown to be protective for perinatal transmission of HIV and the HTLV-1, did not affect perinatal transmission of HCV


- maternal HLA-DRB104 correlated with protection from vertical transmission
- HLA-DRB110 in children was a risk factor
- HLA-DRB1 locus mismatch between mother and child was a protective factor (p=0.017)

Bevilacqua et al. Virology 2009;390:64-70
Breastfeeding

HCV in human milk

- HCV RNA has been detected in breast milk and colostrum

- isolated descriptions of perinatal infections attributed to breast-feeding are available
Breastfeeding

- data based on large cohorts of mothers infected by HCV and their exposed children demonstrated that breast-feeding in the absence of damaged, cracked, or bleeding nipples, does not increase the rate of perinatal transmission of HCV

Resti et al. J Infect Dis 2002;185:567–72
European Paediatric Hepatitis C Virus Network. BJOG 2001;108:371–7
Timing of Mother to Child Transmission of Hepatitis C Virus

Pregnancy 9 months

First 18 months of life

HCV Ab

HCV RNA

NOT INFECTED
# Timing of Mother to Child Transmission of Hepatitis C Virus

<table>
<thead>
<tr>
<th>Pregnancy 9 months</th>
<th>First 18 months of life</th>
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<tbody>
<tr>
<td><strong>HCV Ab</strong></td>
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<thead>
<tr>
<th><strong>HCV RNA</strong></th>
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<td>+</td>
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**INFECTED**
**Strategy for Prevention of HBV Infection**

Red Book, Report of the Committee on Infectious Diseases
American Academy of Pediatrics

- universal immunisation of infants beginning at birth

- prevention of perinatal HBV infection through:
  - routine screening of all pregnant women
  - immunoprophylaxis of infants born to
    - HBsAg-positive women
    - women with unknown HBsAg status

- routine immunisation of children, adolescents and adults
  who previously have not been immunised
Strategy for Prevention of HBV Infection

Red Book, Report of the Committee on Infectious Diseases
American Academy of Pediatrics

- without immunoprophylaxis, up to 90% of infants born to HBeAg-positive mothers become infected.

- maternal screening programs and universal active and passive immunoprophylaxis of newborn have reduced dramatically the HBV transmission rates by 95%
all pregnant women should be tested for HBsAg during an early prenatal visit

testing should be repeated at the time of admission to the hospital for delivery for HBsAg negative women at high risk of HBV infection
Management of Infants Born to HBsAg-Positive Women

Red Book, Report of the Committee on Infectious Diseases
American Academy of Pediatrics

- Infants born to HBsAg-positive mothers should receive the initial dose of hepatitis B vaccine within 12 hours of birth and HBIG (0.5 mL) should be given concurrently but at a different anatomic site.

- The interval of effectiveness of HBIG is unlikely to exceed 7 days.

- Subsequent doses of vaccine should be given as recommended.
Infants Born to Mothers Not Tested During Pregnancy

Red Book, Report of the Committee on Infectious Diseases
American Academy of Pediatrics

- test mother as soon as possible to determine HBsAg status
- while awaiting results, the infants should receive the first HBV vaccine dose within 12 hours of birth
- if the women is HBsAg positive, term infant should receive HBIG within 7 days of birth
- subsequent doses of vaccine should be given as recommended
What About Immunisation Failure?

5% of the children born to HBsAg-positive mothers

- infants born to mothers with very high levels of HBV DNA
- incomplete administration of the regimen of vaccination

- should HBsAg-positive mothers with high levels of viremia be given antiviral therapy during the last trimester in order to reduce the level of virus at the time of delivery, the time at which actual transmission is thought to occur?
Antiviral Treatment and Pregnancy

Patients on Antiviral Therapy for Hepatitis B Are Asked to Practice Birth Control

- interferon has antiproliferative actions and is considered contraindicated during pregnancy

- tenofovir and telbivudine are considered “Category B”, indicating that they have been found to be safe in animal models and there is limited data in humans

- lamivudine, adefovir and entecavir are considered “Category C”, indicating that their safety has not been shown adequately either in animal models or humans
Lamivudine and Perinatal Transmission of HBV

Results

- 8 women with high levels of HBV DNA ($>10^9$ genome equivalents/mL) were treated with lamivudine during the last 6 to 40 days of pregnancy.

- 1/8 children born to treated mothers developed chronic hepatitis B, compared to 7/24 historical controls with similar levels of HBV DNA.

Lamivudine and Perinatal Transmission of HBV

Randomised Controlled Trial

- 150 mothers with HBsAg and high levels of HBV DNA (>10⁹ genome equivalents/mL)

- randomized to receive lamivudine or placebo from week 32 of gestation to 4 weeks postpartum

- evaluating children with complete data 3/49 (6%) infants of mothers given lamivudine compared to 5/41 (12%) given placebo had evidence of HBV transmission (p 0.368).

Xu et al. J Viral Hepat 2009;16:94-103
Lamivudine and Perinatal Transmission of HBV

A Meta-Analysis

- lamivudine from 24 to 32 weeks of gestation, until delivery to 1 month post-delivery

- newborns in the lamivudine treated group had:
  - 13% to 24% lower incidence of intrauterine exposure
  - 1.4% to 2% lower perinatal infection rate at 9 to 12 months

although a high viral load is clearly important, it is not the only factor predisposing to failure of immunoprophylaxis. This is highlighted by a case in which a child developed chronic HBV infection, despite suppression of HBV DNA to undetectable levels in the mother with lamivudine therapy throughout gestation and appropriate immunoprophylaxis after birth.
HBIG in Pregnancy and Perinatal Transmission of HBV

- HBIG administered regularly during late pregnancy is potent to cut down HBV intrauterine infection.

- The possibility of HBV intrauterine infection increases if maternal blood HBV DNA $\geq 10^8$ copies/mL.

Li et al. World J Gastroenterol 2004;10:3215-7
Perinatal Transmission of HBV and Mode of Delivery

Systematic Review

- 942 studies; 938 excluded, 4 studies (n 789), all performed in China, 1 published in English
- Elective caesarian section reduce the rate of mother to child transmission of HBV (ECS: 10.5%; vaginal delivery: 28.0%; RR 0.41, 95% CI 0.28 to 0.60, P < 0.000001)

Yang et al. Virol J 2008;5:100
Breastfeeding

our experience

- 85 infants born to 84 mothers who were hepatitis B surface antigen positive (only 2 HBeAg-positive)
- all infants received immunisation against hepatitis B virus

<table>
<thead>
<tr>
<th></th>
<th>Overall results (n=85)</th>
<th>Breast fed infants (n=22)</th>
<th>Formula fed infants (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants who seroconverted</td>
<td>82 (96.5%)</td>
<td>21 (95.4%)</td>
<td>61 (96.8%)</td>
</tr>
<tr>
<td>Hepatitis B virus infections</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

de Martino et al. Arch Dis Child 1985;60:972-4
**Breastfeeding**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of infants</th>
<th>Population</th>
<th>Prophylaxis</th>
<th>Infected or failed seroconversion to antiHBs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beasley et al.</td>
<td>147</td>
<td>USA, Taiwan (China)</td>
<td>No</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>Tseng et al.</td>
<td>170</td>
<td>Hong Kong (China)</td>
<td>HBIG + Vx</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>de Martino et al.</td>
<td>85</td>
<td>Italy</td>
<td>Vx</td>
<td>4.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Hill et al.</td>
<td>369</td>
<td>USA</td>
<td>HBIG + Vx</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

BF: Breastfeeding; FF: Formula feeding; HBIG: Hepatitis B immune globulin; NS: Nonsignificant.

**Table 1** Safety of breastfeeding in case of chronic hepatitis B virus infection of mothers

Breastfeeding and Treatment

- for mothers on antiviral therapy, breastfeeding is not recommended

- little is known about the extent of exposure of antiviral agents during breastfeeding. Thus, little is known about the overall safety of breastfeeding in this setting.
Agenda della gravidanza: le visite, gli esami e i test

Fonte: “Linee guida per la gravidanza fisiologica”, 2010, Ministero della Salute
First Trimester HCV Ab

HCV Ab positive

TEST HCV RNA

HCV RNA +

HCV RNA -

Three months HCV RNA, LFTs

POSITIVE

CLOSE 3 months follow up

NEGATIVE

18 months HCV Ab
Third trimester HBsAg

- negative
- positive
- Not determined

Immunisation

- HBIG

Check HBsAg
If +, HBIG

Complete immunisation