Perinatal Transmission of Hepatitis C Virus

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VHPB MEETING

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Perinatal Transmission of Hepatitis C Virus

Outline

- definition and timing
- transmission rates
- risk factors
- the Trojan horse hypothesis
- conclusion
Global Burden of HCV in Children and Adolescents

- **13.2 (11.5-21.2) million** children between 1 and 15 years are infected with HCV worldwide

- **6.6 (6.1-11.6) million** viraemic infections

El-Sayed M & Razavi H, EASL 2015
Vertical Transmission of Hepatitis C Virus

Timing

HCV RNA detected by PCR in serum of the neonate/infant

- first 24 hours of life
- weeks after birth

Resti et al. BMJ 1998
Vertical Transmission of Hepatitis C Virus

HCV antibody and RNA-positive women

HIV-negative women

Random effects model

Heterogeneity: I-squared=45.9%, P = .0203

5.8 [4.2; 7.8] 100%

HIV-positive women

Random effects model

Heterogeneity: I-squared=28.8%, P = .1982

10.8 [7.6; 15.2] 100%

Vertical Transmission

Risk factors

- maternal

- obstetric procedures

- factors **NOT** associated with an increased risk
Vertical Transmission

Maternal risk factors

- HCV viraemia
- HIV co-infection
- previous or ongoing history of IVDU
- sexual partner HCV-infected
- active hepatitis
- infection of maternal PBMCs
- presence of the negative strand of HCV inside the PBMC
- HLA class II mother-child concordance

Indolfi et al. J Ped 2013
Vertical Transmission

Obstetric procedures

- invasive internal fetal monitoring
- vaginal or perineal laceration during vaginal delivery
- >6 hours duration of the rupture of membranes
- episiotomy
- amniocentesis

- conditions increasing the intrapartum exposure to maternal blood
- being second twin

Indolfi et al. J Ped 2013
Vertical Transmission

Factors NOT associated with an increased risk

- HCV genotype
- *IL28B (IFNL4)* genotype
- mode of delivery (Caesarean *versus* vaginal)
- type of feeding
- level of viraemia

Indolfi et al. J Ped 2013
HCV Infection in Pregnancy
Viraemia and Transaminases

Gervais et al. J Hepatol 2000
VERTICAL TRANSMISSION OF HCV

- maternal viremia
- prolonged duration of the rupture of membranes
- invasive internal fetal monitoring
- infection of maternal PBMCs
- female sex
- HLA class II compatibility between mother and child
- sexual partner of the mother infected by HCV
- history of intravenous drug use
- coinfection with HIV
- raised aminotransferase levels during the last year before pregnancy and at delivery


Results of Epidemiological Studies

- history of intravenous drug use
- coinfection with HIV
- prolonged duration of the rupture of membranes
- invasive internal fetal monitoring
Results of Multivariate Analyses and Possible Logical Interpretation

VIRTUAL TRANSMISSION OF HCV

- maternal viremia
- infection of maternal PBMCs
- history of intravenous drug use
- sexual partner of the mother infected by HCV
- co-infection with HIV

References:
- Blood, 2000
- J Infect Dis 2002
Results of Multivariate Analyses and Possible Logical Interpretation

VERTICAL TRANSMISSION OF HCV

- maternal viremia
- invasion of maternal PBMCs
- history of intravenous drug use
- sexual partner of the mother infected by HCV
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- HLA class II compatibility between mother and child
- invasive internal fetal monitoring
- co-infection with HIV
HCV MATERNAL QUASISPECIES

Indolfi et al. J Ped 2013
HCV MATERNAL QUASISPECIES

MATERNAL PBMC

Indolfi et al. J Ped 2013
HCV MATERNAL QUASISPECIES

MATERNAL PBMC

Indolfi et al. J Ped 2013
HCV MATERNAL QUASISPECIES

MATERNAL PBMC

CHILD

Indolfi et al. J Ped 2013
Loss of immune escape mutations during persistent HCV infection in pregnancy enhances replication of vertically transmitted viruses

Jonathan R Honegger¹,², Seungtaek Kim³–⁵, Aryn A Price⁶, Jennifer A Kohout¹, Kevin L McKnight³, Mona R Prasad⁷, Stanley M Lemon³,⁸,⁹, Arash Grakoui⁶,¹⁰ & Christopher M Walker¹,²
Honegger RJ, Nature Medicine 2013
Increased serum aminotransferase levels during the past year before pregnancy and at delivery

Increased viral heterogeneity

Sexual partner of the mother infected with HCV

Co-infection with HIV

Maternal history of intravenous drug use

HLA class II compatibility between mother and child

Pregnancy-induced CTL dysfunction and selection of viral quasispecies with enhanced replicative fitness

Transmission of wild-type or revertant viruses coupled with the lack of the restricting maternal HLA class I alleles

Maternal PBMC infection

Perinatal transmission of HCV

Indolfi et al. Nat Rev Gastroenterol Hepatol 2014
Vertical Transmission of Hepatitis C Virus

Conclusion

- maternal HCV viraemia is the limiting condition for vertical transmission

- the use of DAAs during or at the end of pregnancy could significantly impact intrauterine and perinatal transmission of the virus, respectively

- the ultimate mechanism of vertical transmission is still unknown
MEYER CHILDREN’S HOSPITAL

– Elisa Bartolini
– Daniele Serranti
– Chiara Azzari
– Massimo Resti

PENTA

– Claire Thorne
– Carlo Giaquinto
HCV RNA in maternal PBMC is highly associated with transmission of HCV to the newborn

The presence of negative-strand HCV RNA (a marker of HCV replication) in maternal PBMC is associated with perinatal transmission

<table>
<thead>
<tr>
<th>HCV strand</th>
<th>Infants infected (n = 13), no.</th>
<th>Infants not infected (n = 53), no.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>13</td>
<td>13</td>
<td>&lt; .000001</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>0</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Azzari et al. Blood 2000