The use of DAAs in pregnancy in HCV-infected women

19th International Workshop on Clinical Pharmacology of Antiviral Therapy, Baltimore, MD, May 23, 2018

David Burger, PharmD, PhD
david.burger@radboudumc.nl
The future use of DAAs in pregnancy in HCV-infected women

19th International Workshop on Clinical Pharmacology of Antiviral Therapy, Baltimore, MD, May 23, 2018

David Burger, PharmD, PhD
david.burger@radboudumc.nl
Disclosures DM Burger

- Janssen: research grants, advisory board, speaker at symposia
- Merck: research grants, advisory board, speaker at symposia
- Abbvie: advisory board, speaker at symposia
- ViiV Healthcare: research grant, advisory board, speaker at symposia
- Bristol-Myers Squibb: research grants, advisory board, speaker at symposia
- Gilead: advisory board, speaker at symposia

NB all payments have been invoiced by the financial department of Radboudumc
Contents

• Mother-to-child transmission of HCV: epidemiology & risk factors

• HCV infection in pregnant women: should it be treated?

• If treatment with DAAs is indicated during pregnancy:
  • When to start?
  • Only perinatally or also post-natally?
  • Which DAA combination?

• Research priorities

• Conclusions
Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission

D M Gibb, R L Goodall, D T Dunn, M Healy, P Neave, M Cafferkey, K Butler

Summary
Background Little information is available about the timing of mother-to-child transmission of hepatitis C virus (HCV), and no interventions to decrease transmission rates have been identified. We examined the effect of risk factors, including mode of delivery, on the vertical transmission rate.

Methods Data from HCV-infected women and their infants from three hospitals in Ireland and from a British Paediatric Surveillance Unit study of infants born to HCV-infected mothers were used to estimate the vertical transmission rate and risk factors for transmission. We used a probabilistic model using methods that simultaneously estimated the time to HCV-antibody loss in uninfected infants and the diagnostic accuracy of PCR tests for HCV RNA.

Findings 441 mother-child pairs from the UK (227) and Ireland (214) were included. 50% of uninfected children became HCV-antibody negative by 8 months and 95% by 13 months. The estimated specificity of PCR for HCV RNA was 97% (95% CI 96–99) and was unrelated to age; sensitivity was only 22% (7–46) in the first month but rose sharply to 97% (85–100) thereafter. The vertical transmission rate was 6-7% (4.1–10.2) overall, and 3.8 times higher in HIV coinfected (n = 22) than in HIV-negative women after adjustment for other factors (p = 0.06). No effect of breastfeeding on transmission was observed, although only 59 women breastfed. However, delivery by elective caesarean section before membrane rupture was associated with a lower transmission risk than vaginal or emergency caesarean-section delivery (odds ratio 0 [0.0–0.87], p = 0.04, after adjustment for other factors).

Interpretation The low sensitivity of HCV RNA soon after birth and the finding of a lower transmission rate after delivery by elective caesarean section suggest that HCV transmission occurs predominantly around the time of delivery. If the findings on elective caesarean section are confirmed in other studies, the case for antenatal HCV testing should be reconsidered.

Introduction Prospective studies of mother-to-child (vertical) transmission of hepatitis C virus (HCV) infection have reported average transmission rates of about 5% in women with HCV alone and 15% in women coinfected with HIV, but the rates vary widely between studies. The presence in the mother of HCV RNA as shown by PCR is a risk factor for transmission.

Much knowledge has accumulated about the mechanisms and timing of vertical HIV transmission, and important roles of breastfeeding and mode of delivery have been identified. Most transmission is known to occur around the time of delivery, and elective caesarean-section delivery undertaken before membrane rupture lowers vertical transmission rates compared with emergency caesarean-section or vaginal delivery. In contrast, current understanding of the epidemiology of vertical HCV infection is limited. Vertical transmission rates are similar among breastfed and bottle-fed infants. Of the few studies that have examined the effect of mode of delivery on transmission, only one reported significantly lower transmission rates with caesarean-section delivery. However, no study differentiated between emergency and elective caesarean section, and there are few data on the relative importance of transmission during the intrapartum and intrapartum periods.

We report the results of a large cohort of children born to HCV-infected women in the UK and Ireland, with particular emphasis on the role of mode of delivery on vertical transmission of HCV.

Methods
Patients Two sources of data were merged. First, from January, 1994, to April, 1999, data were prospectively gathered on all infants born to pregnant women with known HCV infection attending three hospitals in Dublin, Ireland. Women were offered testing during pregnancy if they requested testing. Second, between March, 1997, and April, 1999, all consultant paediatricians in the UK and Ireland were asked to report all children with HCV...
Epidemiology of HCV in pregnancy

- About 1-8% of pregnant women has HCV infection
- MTCT of HCV is considered to be low (2-11%), but
  - Recent estimate: 4,000 newborns with HCV per year in the US (underestimation?)
  - Egypt: 3,000 – 5,000 HCV+ newborns in a 2008 birth cohort
  - Maternal HCV infection is associated with negative health outcomes for the newborn: preterm birth, low birth weight
  - Maternal HCV infection is associated with negative health outcomes for the woman: intrahepatic cholestasis of pregnancy (ICP); incidence in non-HCV infected women is 0.2-2.5%; this may increase 20-fold when the woman is HCV infected
  - Prevention of MTCT of HCV should become an important part of HCV elimination strategies

- HIV/HCV co-infection doubles the risk of MTCT of HCV (5.8% → 10.8%)

- Uncertainty about timing of transmission: in utero (30-50%) and/or at labor?

Benova et al. CID 2014;
Some arguments against PMTCT of HCV

- HCV-infected women can be treated after delivery (no risk of adverse events to the fetus or newborn)
- MTCT is relatively low (when compared to HIV or HBV)
- Newborns that may become infected have a chance for spontaneous clearance
- HCV-infected children can be treated after approval of pediatric formulations and doses of DAAs
  - Harvoni® licensed for children >12 years of age or with BW>35kg
  - SOF/LED and GP being tested for children 3-12 years of age (clinicaltrials.gov)
Some arguments *in favor of* PMTCT of HCV

- Many HCV-infected pregnant women (and their children!) will be lost to follow-up after delivery
- Pregnancy is an opportunity to cure the HCV infected woman (and prevent MTCT to the newborn); also part of elimination strategy!
- HCV infected children cannot be treated before age of 12 now; although severe liver disease may be rare in children, extrahepatic manifestations may exist undetected (e.g. fatigue).
- HCV infected children may transmit HCV to others (playground, family)
- Current DAA regimens are pangenotypic and short, so avoiding exposure to DAAs in 1st trimester is not difficult
Hepatitis C in Pregnancy in the Era of Direct-acting Antiviral Treatment: Potential Benefits of Universal Screening and Antepartum Therapy

HELENE B. BERNSTEIN, MD, PhD,*, JEFFREY C. DUNKELBERG, MD, PhD,† and KIMBERLY K. LESLIE, MD‡

CLINICAL OBSTETRICS AND GYNECOLOGY
Volume 61, Number 1, 146–156
Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

Hepatitis C in pregnancy: screening, treatment, and management

Society for Maternal-Fetal Medicine (SMFM); Brenna L. Hughes, MD, MSc; Charlotte M. Page, MD; Jeffrey A. Kuller, MD

The American College of Obstetricians and Gynecologists (ACOG) endorses this document.

Society for Maternal-Fetal Medicine (SMFM) Consult Series | #43
smfm.org

Hepatitis C in Pregnancy: Review of Current Knowledge and Updated Recommendations for Management

Charlotte M. Page, MD,* Brenna L. Hughes, MD, MSc,† Eleanor H.J. Rhee, MD,‡ and Jeffrey A. Kuller, MD§

Volume 72, Number 6
OBSTETRICAL AND GYNECOLOGICAL SURVEY
Copyright © 2017 Wolters Kluwer Health,

Review article

Mother-to-child transmission of hepatitis C virus

Henrique Pott Junior*a,*, Matheus Theodoro*b, Juliana de Almeida Vespoli*b, Jorge Figueiredo Senisea, Adauto Casteloa


CrossMark
Initiate or defer DAAs in pregnancy?

<table>
<thead>
<tr>
<th>Consider Antepartum Treatment</th>
<th>Defer Antepartum Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of fetal harm has been documented using the newly approved DAAs—most are pregnancy category B.</td>
<td>Unproven risk of fetal harm</td>
</tr>
<tr>
<td>The incidence of hepatitis C is on the rise, disproportionately affecting women of child-bearing age.</td>
<td>Pregnancy-associated pharmacokinetic changes could reduce treatment effectiveness.</td>
</tr>
<tr>
<td>Many medications used in pregnancy lack FDA approval.</td>
<td>Clinical trial now ongoing for DAAs; should await results.</td>
</tr>
<tr>
<td>Women are already engaged in care, and may not be under regular medical care at any other time in their lives.</td>
<td></td>
</tr>
<tr>
<td>Women may lose insurance coverage to cover DAA treatment after pregnancy.</td>
<td></td>
</tr>
<tr>
<td>50% of women scheduled for postpartum treatment are lost to follow-up.</td>
<td></td>
</tr>
<tr>
<td>SVR during pregnancy is likely to reduce perinatal HCV transmission.</td>
<td></td>
</tr>
<tr>
<td>SVR may decrease the likelihood of complications associated with active HCV infection including preterm birth, low birth weight and intrahepatic cholestasis.</td>
<td></td>
</tr>
<tr>
<td>Risk of vertical transmission is not limited to delivery. New data indicate that maternal to fetal transmission may occur as early as the first trimester of pregnancy, and more cases occur by the third trimester.</td>
<td></td>
</tr>
<tr>
<td>It is reported that 4000 children are born each year with hepatitis C as a result of vertical transmission, and this number is likely a significant underrepresentation of the true incidence.</td>
<td></td>
</tr>
<tr>
<td>The majority of neonates delivered in the setting of maternal hepatitis C infection do not receive the CDC-recommended screening and follow-up to identify infection.</td>
<td></td>
</tr>
</tbody>
</table>

 Berniein et al 2018
## Safety of DAAs in pregnancy

### How relevant is this when treatment with DAAs is initiated late in pregnancy?

**Table 1: Use of Direct-Acting Antiviral Formulations**

<table>
<thead>
<tr>
<th>Drug Formulation</th>
<th>FDA Pregnancy Category*</th>
<th>Genotype Efficacy†</th>
<th>Details of Use†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>B</td>
<td>All</td>
<td>Must be used with ribavirin or another DAA</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir</td>
<td>B</td>
<td>1, 4</td>
<td>Must be used with ribavirin or dasabuvir</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Unclassified (projected category B)</td>
<td>1, 2, 3</td>
<td>Must be used with sofosbuvir, with or without ribavirin</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Unclassified (projected category B)</td>
<td>1, 4, 5, 6</td>
<td>Must be used with sofosbuvir, with or without ribavirin</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>Unclassified (projected category B)</td>
<td>All</td>
<td>Must be used with sofosbuvir</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavirdasabuvir</td>
<td>Unclassified (projected category B)</td>
<td>1</td>
<td>Must be used with sofosbuvir, with or without ribavirin</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>Unclassified (projected category B)</td>
<td>1, 4</td>
<td>Must be used with sofosbuvir, with or without ribavirin</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Unclassified (projected category C)</td>
<td>1</td>
<td>Must be used with sofosbuvir, with or without ribavirin</td>
</tr>
</tbody>
</table>

†Source: Joint panel from the AASLD and the IDSA.4

**Glecaprevir/pibrentasvir: unclassified (projected cat B)**

**EMA: additional safety concerns for GLE and DAC**

PK Research priorities

• What is the influence of pregnancy on the pharmacokinetics of DAA therapy? In other words, is the standard dose for non-pregnant patients sufficient for pregnant women too?

• Do DAAs cross the placenta?

• Do DAAs transfer into breastmilk and what is the exposure of the infant during breastfeeding?

• Non-PK, but at least as important:
  • What is the safety of DAA therapy for both mother and child? Are some DAA combinations more safe than others?
  • What is the optimal timing for DAA treatment in pregnancy?
Physiological changes in pregnancy may affect total ($C_{tot}$) and free drug concentrations ($C_{free}$) >> risk of lower exposure
ClinicalTrials.gov Identifier: NCT02683005

Sponsor: Catherine Chappell
Collaborators: Gilead Sciences
University of Nebraska

Information provided by (Responsible Party): Cathcrinc Chappell, University of Pittsburgh

Study Design

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Interventional  (Clinical Trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Enrollment</td>
<td>15 participants</td>
</tr>
<tr>
<td>Intervention Model</td>
<td>Single Group Assignment</td>
</tr>
<tr>
<td>Masking</td>
<td>None (Open Label)</td>
</tr>
<tr>
<td>Primary Purpose</td>
<td>Treatment</td>
</tr>
<tr>
<td>Official Title</td>
<td>Phase I Pharmacokinetic and Safety Trial of Ledipasvir/Sofosbuvir Fixed Dose Combination in Pregnant Women With Chronic Hepatitis C Virus Infection</td>
</tr>
<tr>
<td>Study Start Date</td>
<td>September 2016</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>September 2019</td>
</tr>
<tr>
<td>Estimated Study Completion Date</td>
<td>September 2019</td>
</tr>
</tbody>
</table>
Example of PK changes

Mean tenofovir concentrations

CL/F 30%

Colbers A. et al., AIDS, 2013
Ex vivo placental perfusion model

Schalkwijk et al. JAC 2016
Choice of DAA

• Mavy(i)ret (glecaprevir/pibrentasvir) – pan-genotypic
  • GT3 – 16 weeks / all other 8 weeks

• Sof/dac 12 weeks GT1-4
• Sof/led 12 weeks GT 1, (3), 4, , 6

• Epclusa (velpatasvir and sofosbuvir) – Pangenotypic
  Gilead - no option

  • Velpatasvir had no adverse effects on mating and fertility. No teratogenic effects were observed in the mouse and rat developmental toxicity studies with velpatasvir at AUC exposures approximately 31- and 6--fold higher, respectively, than the human exposure at the recommended clinical dose. **However, a possible teratogenic effect was indicated in rabbits where an increase in total visceral malformations was seen in exposed animals at AUC exposures up to 0.7 fold the human exposure at recommended clinical dose.** The human relevance of this finding is not known. Velpatasvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study at AUC exposures approximately 5-fold higher than the human exposure at the recommended clinical dose.
# Choice of DAA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genotype</th>
<th>Animal data</th>
<th>Predicted PK change</th>
<th>Potential use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>Pan-genotypic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Genotype 1, 4</td>
<td></td>
<td>CYP3A4 activity ↑</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir(^a)</td>
<td>Genotype 1-4</td>
<td>FDA, EMA</td>
<td>CYP3A4 activity ↑</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir(^b)</td>
<td>Genotype 1,4-6</td>
<td></td>
<td>pH increase</td>
<td></td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>Pan-genotypic</td>
<td></td>
<td>pH increase, CYP3A4 activity ↑</td>
<td></td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>Genotype 1,4</td>
<td></td>
<td>CYP3A4 activity ↑</td>
<td></td>
</tr>
<tr>
<td>Elbasvir</td>
<td>Genotype 1,4</td>
<td></td>
<td>CYP3A4 activity ↑</td>
<td></td>
</tr>
<tr>
<td>Glecaprevir</td>
<td>Pan-genotypic</td>
<td>FDA, EMA</td>
<td>CYP3A4 activity ↑</td>
<td></td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>Pan-genotypic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voxilaprevir</td>
<td>Pan-genotypic</td>
<td></td>
<td>CYP3A4 activity ↑</td>
<td></td>
</tr>
</tbody>
</table>
Some thoughts about study design

• Proposal: randomized study:

- Pregnancy
  - 8 weeks DAA, trt preg
    - start wk 23-28
  - 8 weeks DAA, trt peripartum
    - start week 35
- Delivery
  - 12 weeks DAA, trt preg
    - start week 20-23
  - 12 weeks DAA, trt peripartum
    - start week 35

PK curves, 10 samples

Cord blood
Partnership to cure hepatitis C virus (HCV) in mono- and HIV/HCV co-infected pregnant women
And prevent VERTical HCV transmission

HCVAVERT
Ultimate aim

• To conduct a trial of DAAs in the 3rd trimester of pregnancy to cure mothers & prevent transmission
• Arms: ≥28 weeks vs delivery vs post-partum ?
• Outcome: SVR12 and/or retention and/or safety ?
Study team and key collaborators

- UK:
  - UCL: Judd, Collins, Gibb, Ford, Nastouli, Pett, Thorne, Turkova
  - Bristol: Ades
- Egypt: El-Sayed, Mohamed
- Ukraine: Malyuta, Volokha
- Netherlands: Burger, Colbers
- France (INSERM): Yazdanpanah, Deuffic-Burban
- Italy (Meyer Children’s Hospital): Indolfi
Study objectives

1: Timing and risk factors for MTCT
   1A: Gather evidence from existing studies
   1B: Develop model of timing of MTCT

2: Choice of DAA regimen
   2A: Review evidence for safety
   2B: Establish prospective registry in Egypt

3: Cost-effectiveness
   3A: Adapt existing model to pregnancy
   3B: Review evidence to parameterise model
   3C: Conduct scenario analysis

4: Key implementation questions
   4A: Current practice – screening, care, diagnostics
   4B: DAA acceptability survey
Accessibility, use and price of DAAs

- Review literature, consult local partners, DNDi, MSF, MPP, CDAF

### TABLE 1: PRICES FOR AVAILABLE ORIGINATOR AND GENERIC DAAS IN SELECTED MIDDLE-INCOME COUNTRIES (IN $US PER 28-TAB BOTTLE)

<table>
<thead>
<tr>
<th>COUNTRY*  (Income Classification)</th>
<th>GILEAD SOF²⁵</th>
<th>GENERIC SOF</th>
<th>GILEAD SOF/LDV²⁵</th>
<th>GENERIC SOF/LDV</th>
<th>GILEAD SOF/VEL²⁵</th>
<th>GENERIC SOF/VEL</th>
<th>BMS DCV 60MG</th>
<th>GENERIC DCV 60MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil¹ (UMIC)</td>
<td>$2,292</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$850</td>
<td></td>
</tr>
<tr>
<td>Egypt (LMIC)</td>
<td>$250</td>
<td>$51⁽⁴⁾</td>
<td>$300</td>
<td>--⁽ᵗ⁾</td>
<td></td>
<td></td>
<td>$167⁽¹⁾</td>
<td>$7⁽⁴⁾</td>
</tr>
<tr>
<td>India (LMIC)</td>
<td>$250</td>
<td>$22⁽⁴⁾</td>
<td>$300</td>
<td>$65⁽⁴⁾</td>
<td></td>
<td>$283⁽²⁶⁾</td>
<td>$167⁽²⁷⁾</td>
<td>$13⁽⁴⁾</td>
</tr>
<tr>
<td>Jordan²⁸ (UMIC)</td>
<td></td>
<td></td>
<td>$22,220</td>
<td></td>
<td></td>
<td></td>
<td>$11,800</td>
<td>$11,800</td>
</tr>
<tr>
<td>Malaysia²⁹ (UMIC)</td>
<td>$11,053</td>
<td>$14,212</td>
<td>$18,239</td>
<td></td>
<td></td>
<td></td>
<td>$3,746</td>
<td>$3,746</td>
</tr>
<tr>
<td>Pakistan (LMIC)</td>
<td>$250</td>
<td>$15⁽¹⁾</td>
<td>--⁽ᵗ⁾</td>
<td></td>
<td></td>
<td></td>
<td>$1,500⁽³⁰⁾</td>
<td></td>
</tr>
<tr>
<td>Thailand⁷³,⁽¹⁾ (UMIC)</td>
<td>$1,200</td>
<td>$2,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1,500⁽³⁰⁾</td>
<td></td>
</tr>
<tr>
<td>Ukraine (LMIC)</td>
<td>$250</td>
<td>$300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$300⁽³¹⁾</td>
<td></td>
</tr>
</tbody>
</table>

* Included in both BMS and Gilead voluntary licences: Egypt, India, Pakistan; included in Gilead voluntary license only: Malaysia, Thailand, Ukraine; excluded from both BMS and Gilead voluntary licenses: Brazil, Jordan.

† Generic SOF/LDV available; price not reported.

§ SOF and SOF/LDV prices are for the private market. Thailand was recently added to Gilead’s VL, but reduced price is not yet available.

Boxes shaded in grey indicate that the DAAs are not available in that country. All prices converted to USD using Oanda: https://www.oanda.com

UMIC = upper middle-income country; LMIC = lower middle-income country.
Conclusions

• At this moment, the field appears not yet ready for treatment of HCV in pregnancy

• But awareness increases, at least among obstetricians

• One could argue that HIV/HCV co-infected pregnant women have a higher priority for DAA treatment during pregnancy

• If placental passage has been assessed ex vivo, is this a favorable characteristic for a DAA? (pre-exposure prophylaxis vs. AEs in the newborn)

• Uncontrolled treatment of HCV-infected pregnant women should be discouraged (it’s not HIV)
Thank you for your attention and greetings from Nijmegen!