



Perinatal Transmission of Hepatitis C

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Project ECHO HCV Collaborative

Conflict of Interest Disclosure Statement

Speaker Bureau: AbbVie, Gilead, Intercept, Merck, Salix/Valeant

Consultant/Advisory Board : AbbVie, Gilead, Intercept

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LEARNING OBJECTIVES

1. Understand the frequency of vertical transmission of HCV from HCV infected mother to fetus/infant
2. Define the risk factors for vertical transmission of HCV
3. Determine how to diagnose active HCV in the newborn

Hepatitis C Infection in Children

- Worldwide, **hepatitis B and C** are the **most common causes of chronic viral hepatitis in children and adults** [[1](#)].
 - Effective vaccination programs against hepatitis B
- **Hepatitis C virus (HCV)** has become the **primary cause of chronic viral hepatitis in children** [[2](#)]
- **Vertical transmission** the leading source of infection [[3-5](#)]
- Vertical transmission refers to viral transmission
 - from the mother to the infant during pregnancy
 - at the time of delivery
 - during the first 28 days after birth

1. [Williams R. Global challenges in liver disease. Hepatology 2006; 44:521.](#)

2. [Slowik MK, Jhaveri R. Hepatitis B and C viruses in infants and young children. Semin Pediatr Infect Dis 2005; 16:296.](#)

3. [Bortolotti F, Resti M, Giacchino R, et al. Changing epidemiologic pattern of chronic hepatitis C virus infection in Italian children. J Pediatr 1998; 133:378.](#)

4. [Bortolotti F, Iorio R, Resti M, et al. An epidemiological survey of HCV infection in Italian children in the decade 1990-1999. J Pediatr Gastroenterol Nutr 2001; 32:562.](#)

5. [Bortolotti F, Iorio R, Resti M, et al. Epidemiological profile of 806 Italian children with hepatitis C virus infection over a 15-year period. J Hepatol 2007; 46:783.](#)

Potential Risk for HCV Vertical Transmission

- Vertical transmission occurs in 5.8% (3%-13%) of infants born to women who are infected only with HCV
 - Twice as often in women who are HCV/HIV coinfectd (2)
 - or who have high HCV viral loads (3)
- There is currently no recommended intervention to prevent transmission of infection from mother to child (3)
- Increased reported incidence of HCV infection among persons ≤ 30 yo with similar increases among women and men in this age group
- Increased concern re: number of pregnant women with HCV infection, & in the number of infants who could be exposed to HCV at birth.

1. Koneru A, et al. Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission — United States and Kentucky, 2011–2014. MMWR Morb Mortal Wkly Rep 2016;65:705–710.
2. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis 2014;59:765–73.
3. Kanninen TT, Dieterich D, Asciutti S. HCV vertical transmission in pregnancy: new horizons in the era of DAAs. Hepatology 2015;62:1656–8.

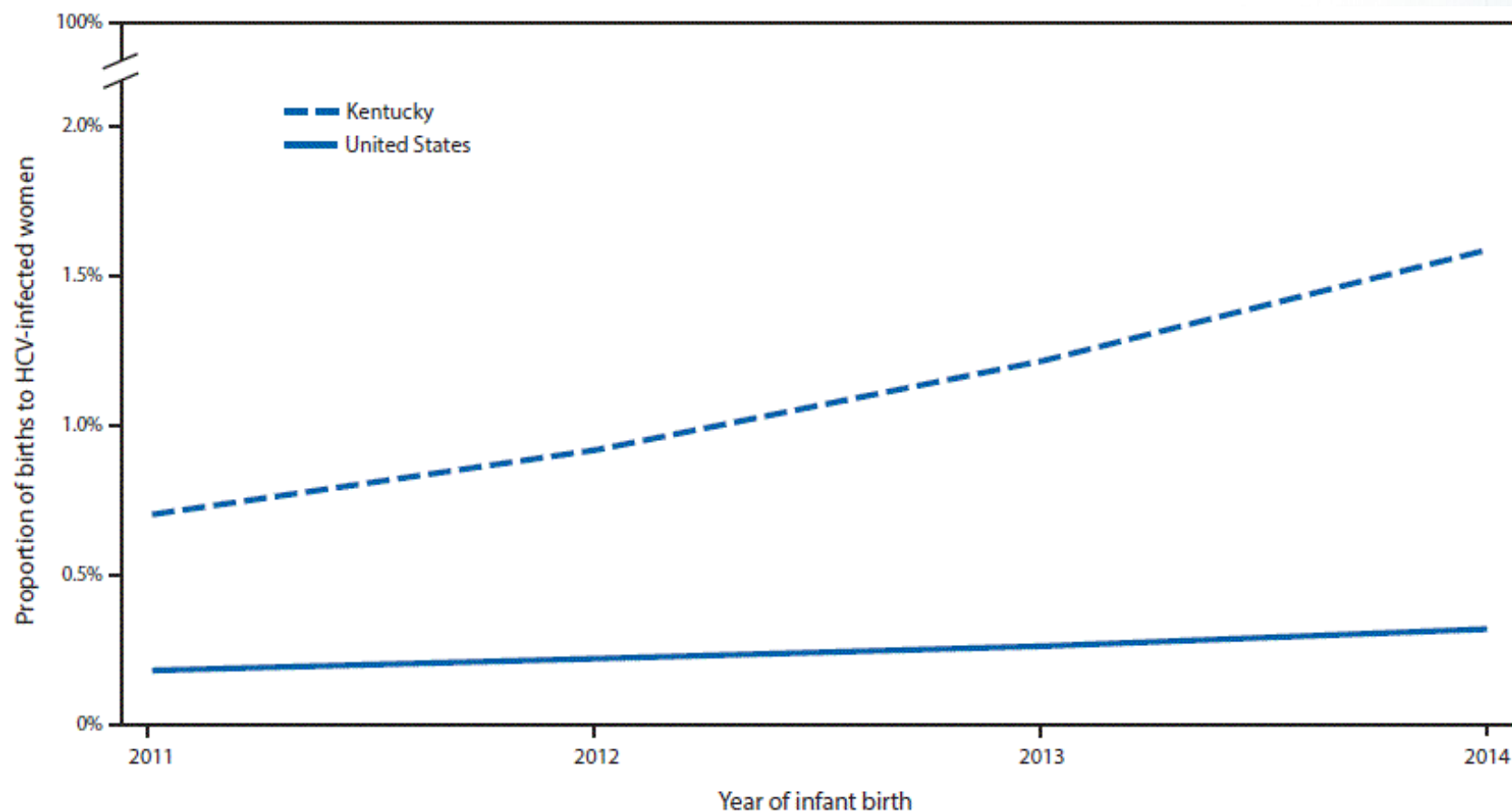
Potential Risk for HCV Vertical Transmission — United States and Kentucky, 2011–2014

- Recent increases in injection drug use --> increases in incidence of HCV infection among young persons
- During 2011–2014, increased rates of HCV detection (antibody or RNA positivity) among women of childbearing age
 - Nationally- 22% (1.4% to 1.7%)
 - Kentucky - >200% (2.75% to 5.6%)
- Birth certificate data showed the proportion of infants born to HCV-infected mothers increased during same period (~4,000,000 births per year)
 - Nationally- 68% (0.19% to 0.32%)
 - Kentucky - 124% (0.71% to 1.59%)

Koneru A, et al. Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission — United States and Kentucky, 2011–2014. MMWR Morb Mortal Wkly Rep 2016;65:705–710.

Potential Risk for HCV Vertical Transmission — United States and Kentucky, 2011–2014

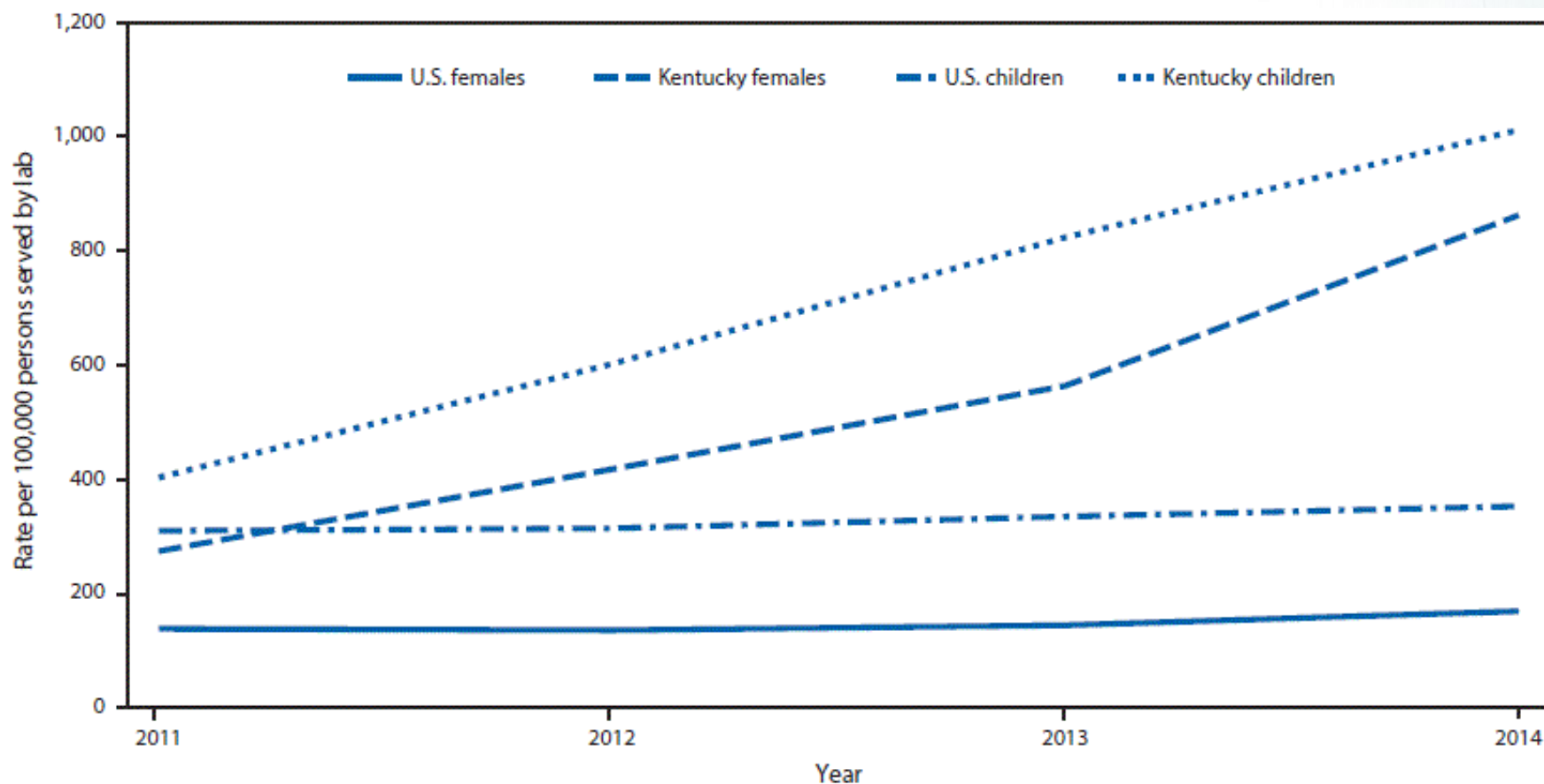
Proportion of infants born to hepatitis C virus (HCV)-infected women



Koneru A, et al. Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission — United States and Kentucky, 2011–2014. *MMWR Morb Mortal Wkly Rep* 2016;65:705–710.

Potential Risk for HCV Vertical Transmission — United States and Kentucky, 2011–2014

Hepatitis C virus (HCV) detection rate among females aged 15–44 years
and HCV testing rate among children aged ≤ 2 years



Koneru A, et al. Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission — United States and Kentucky, 2011–2014. MMWR Morb Mortal Wkly Rep 2016;65:705–710.

Hepatitis C in Pregnancy

- Anti-HCV positivity was found in (370) 2.4% of 15,250 pregnant women studied in Italy
 - presence of anti- HCV was tested by means of EIA III
 - 72% were HCV-RNA-positive
- ALT, HIV Ab, and HCV-RNA tested during the 1st month & 3rd trimester of pregnancy, and 6 mo. after delivery
- proportion of anti-HCV- and HCV RNA positive newborns was 5.1% after 1 year (8 of 155)
 - All had same genotype as mother
- Rate of HCV transmission was not affected by the
 - type of delivery or
 - breastfeeding, or the
 - HIV status of the mother

D. Conte, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology*, 31 (2000), pp. 751–755

Hepatitis C in Pregnancy

Risk Factors for Vertical Transmission

- 78 HCV-positive/HIV-negative women with offspring in prospective study to define the prevalence of and risk factors for HCV vertical transmission
- Infants tested for ALT and HCV-RNA at birth and at 4, 8, 12, 18, and 24 months of age
- 8 of 60 (13.3%) infants born to HCV-RNA positive mothers acquired HCV infection
 - High maternal viral load ($P < 0.05$),
 - Maternal HCV risk factors ($P < 0.004$) and
 - History of intrapartum blood transfusion ($P < 0.05$) were associated with increased risk of HCV vertical transmission.
- Only 2 (3.3%) were still infected by the end of follow-up
 - Infants' genotypes matched that of the mothers.
 - ALT levels were in the normal range in all study subjects throughout follow-up.

O. Ceci, et al. Vertical transmission of hepatitis C virus in a cohort of 2447 HIV-seronegative pregnant women: a 24-month prospective study.
J. Pediatr. Gastroenterol. Nutr., 33 (2001), pp. 570–575

Hepatitis C in Pregnancy

Risk Factors for Vertical Transmission

- Conclusions:
- Although vertical transmission from HIV-negative mothers occurs in 13% of cases, there is a high rate of spontaneous viral clearance (75%).
- High maternal viral load and mothers belonging to HCV risk categories were the only variables predictive of the vertical transmission.

O. Ceci, et al. Vertical transmission of hepatitis C virus in a cohort of 2447 HIV-seronegative pregnant women: a 24-month prospective study
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Hepatitis C in Pregnancy: Risk Factors for Vertical Transmission and Natural Hx of HCV Infection Acquired in Infancy

- 244 infants born to HCV Ab-positive mothers were followed from birth until age 12 months
- Maternal serum was collected at enrollment and delivery
- Infant serum was collected @ birth and at 8 well-child visits.
- Testing included:
 - HCV Ab
 - HCV RNA (190/244 {78%} had detectable RNA at delivery)
 - Genotype determination
- HCV-infected infants were followed annually until age 5 yr

Eric E. Mast, et al. Risk Factors for Perinatal Transmission of Hepatitis C Virus (HCV) and the Natural History of HCV Infection Acquired in Infancy
JID 2005:192 (1 December) • 1880-1889

Hepatitis C in Pregnancy: Risk Factors for Vertical Transmission and Natural Hx of HCV Infection Acquired in Infancy

- 9 of 190 (4.7%) infants born to mothers who were HCV RNA positive at delivery became infected
- Transmission rate-
 - 3.8% (7) of the 182 who were HIV negative
 - 25.0% (2) of the 8 who were HIV positive
- 3 (33%) infected infants became HCV RNA negative
- Multivariate analysis: High rates of transmission assoc. with
 - membrane rupture >6 h (odds ratio [OR], 9.3)
 - internal fetal monitoring (OR, 6.7)

Eric E. Mast, et al. Risk Factors for Perinatal Transmission of Hepatitis C Virus (HCV) and the Natural History of HCV Infection Acquired in Infancy
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Hepatitis C in Pregnancy:

Addressing Risk Factors for Vertical Transmission

- Perinatal infection generally occurs during intrapartum period
- Suggested intra-partum management
 - Avoid fetal scalp monitoring
 - Consider cesarean section>
 - Early post membrane rupture
 - Elective, especially in HCV/HIV coinfecting mothers

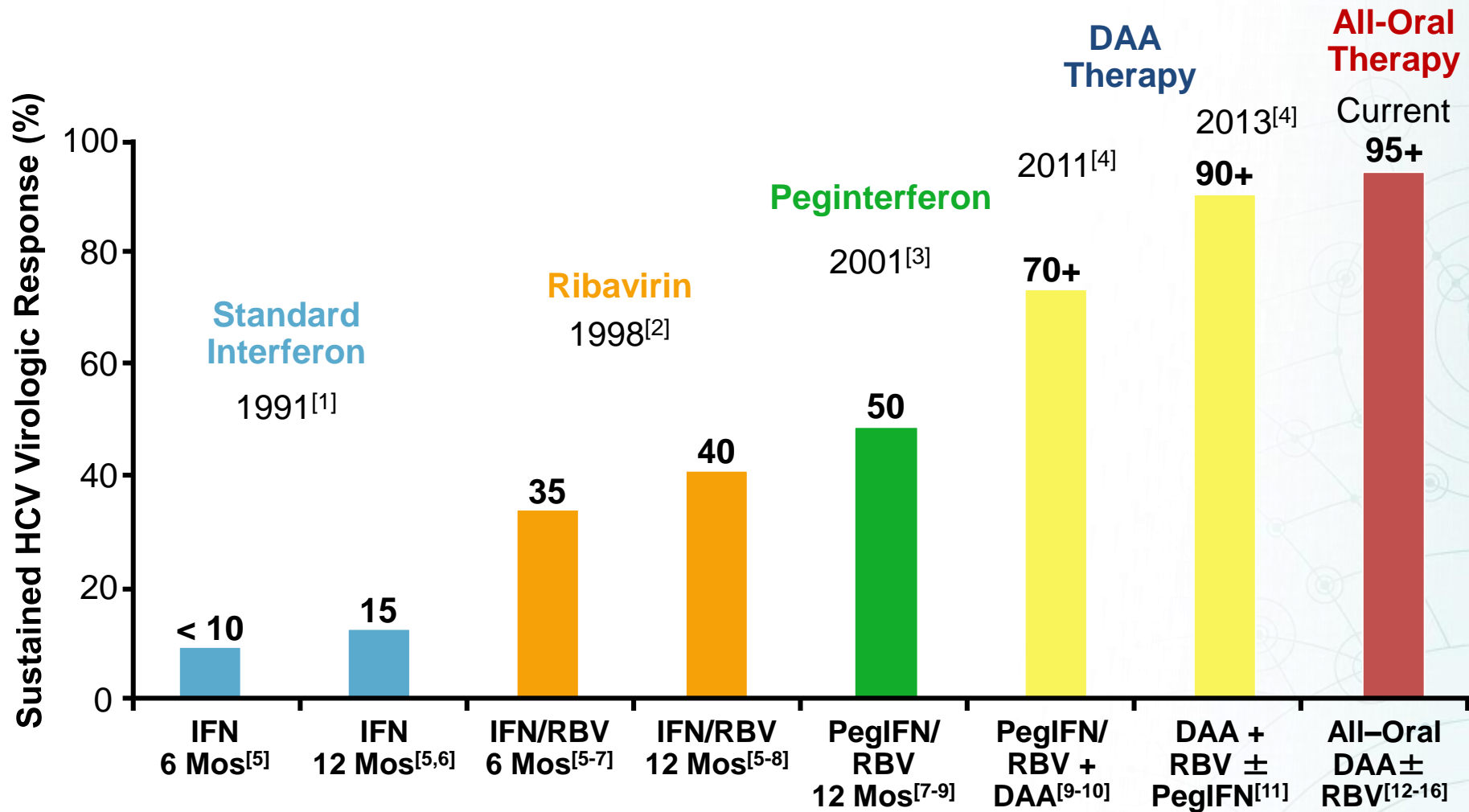
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Hepatitis C in Pregnancy:

Natural Hx of HCV Infection Acquired in Infancy

- Recommended screening and follow-up of infants born to HCV infected mothers
 - RNA testing on 2 occasions between ages 2 and 6 months (preferred)
 - HCV Ab testing >18 months (avoids detection of passively transferred maternal HCV Ab)
- Clinical course of infected infants
 - No clinical hepatitis
 - Transient ALT abnormalities
 - High rate of spontaneous resolution of infection (25%—75%)
- No evidence that breastfeeding spreads HCV
 - HCV RNA in breast milk of 19/37 (51%) mothers who provided samples
 - Presence of HCV RNA in breast milk not related to maternal viral load

Current HCV All-Oral Therapies: Highly Effective, Simple, Well Tolerated



HCV Vertical Transmission in Pregnancy: New Horizons in the Era of DAAs

Table 1. Safety Profile of New DAAs in Pregnancy

DAA Combination	Pregnancy Category
(1) Paritaprevir* + (2) ombitasvir*	(1) B, (2) B
(1) Paritaprevir* + (2) dasabuvir* + (3) ombitasvir*	(1) B, (2) B, (3) B
(1) Daclatasvir [†] + (2) asunaprevir [‡]	(1) N/A, (2) N/A
(1) Daclatasvir [†] + (2) asunaprevir [‡] + (3) beclabuvir	(1) N/A, (2) N/A, (3) N/A
(1) Sofosbuvir* + (2) ledipasvir*	(1) B, (2) B
(1) Sofosbuvir* + (2) ledipasvir* + (3) vedoprevir	(1) B, (2) B, (3) N/A
(1) Sofosbuvir* + (2) ledipasvir* + (3) GS-9669	(1) B, (2) B, (3) N/A
(1) Sofosbuvir* + (2) simeprevir*	(1) B, (2) C
(1) Grazoprevir, (2) elbasvir	(1) N/A, (2) N/A
(1) Daclatasvir [†] + (2) sofosbuvir*	(1) N/A, (2) B
(1) Sofosbuvir* + (2) velpatasvir	(1) B, (2) N/A
(1) Grazoprevir, (2) elbasvir ± (3) MK-3682	(1) N/A, (2) N/A, (3) N/A

*FDA-approved DAA.

[†]Approved in Europe, Brazil, and Japan.

[‡]Approved in Japan.

Abbreviation: N/A, not available.

PREGNANCY CATEGORY B

No risk in other studies: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

PREGNANCY CATEGORY C

Risk not ruled out: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

HCV Vertical Transmission in Pregnancy: Parallels With HIV Therapy in Pregnancy

- Currently used ART for HIV in pregnancy have resulted in dramatic reductions in disease associated maternal-fetal morbidity and mortality
- Majority of antiviral drugs used in HIV, with the exception of efavirenz, are safe throughout pregnancy and their benefits far outweigh any risks.
- Zidovudine, a polymerase inhibitor, routinely used in pregnancy:
Significantly reduces the risk of vertical HIV transmission safely
- Hepatotoxicity and teratogenicity are the main concerns with nucleoside reverse transcriptase inhibitors.
- Protease inhibitor safety profile in pregnancy, particularly in regard to the risk of preterm birth, has been raised
- NS5A inhibitors are not used in HIV treatment, but their profile in pregnancy is promising for possible use in HCV infected mothers

Kanninen TT, Dieterich D, Asciutti S. HCV vertical transmission in pregnancy: new horizons in the era of DAAs. Hepatology 2015;62:1656–8.

HCV Vertical Transmission in Pregnancy: New Issues in the Era of DAAs

- Is it time to initiate routine screening for HCV in all pregnancies?
- What measures are appropriate to diminish risk of vertical transmission of HCV?
 - Should cesarean section for non-obstetric indication be considered?
- Can we justify treating HCV during pregnancy?
 - If so, what would we use and when would we treat?