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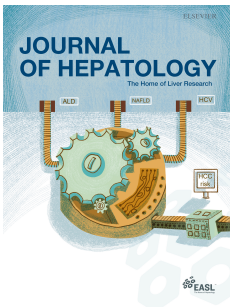

Changing epidemiology, implications, and recommendations for Hepatitis C in Women of Childbearing Age and During Pregnancy

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"Focused Review"

Changing epidemiology, implications, and recommendations for Hepatitis C in Women of Childbearing Age and During Pregnancy

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Tatyana Kushner served on an advisory board for Gilead.
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Key Points:

1. **The incidence and prevalence of HCV infection in women of childbearing age and in pregnancy have demonstrated have increased and have been linked with injection drug use**
2. **Incidence of mother-to-child transmission of HCV may not be adequately described with retrospective studies due to incomplete follow up of infants for testing at 18 months and therefore missing data on rates of tranmission**
3. **Other than HIV suppression in HIV/ HCV co-infected women, there are no known interventions to decrease the risk of MTCT of HCV**
4. **HCV in pregnancy is associated with preterm birth and intrahepatic cholestasis of pregnancy**
5. **Universal screening during pregnancy is supported by the CDC, USPFTF and found cost-effective**

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Brief Summary:
Despite remarkable advances in HCV treatment with DAAs, HCV remains a public health concern worldwide, and rising prevalence of HCV infection has been cited in women of childbearing age. Implications of active HCV on pregnancy include association with cholestasis of pregnancy as well as risk of mother-to-child transmission. Recent updates have increased recommendations for universal screening during pregnancy. Treatment of HCV in the pregnancy context is currently being investigated.

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Hepatitis C in Women of Childbearing Age and During Pregnancy

Introduction

Hepatitis C (HCV) remains a significant public health problem with an estimated 71 million people affected worldwide as of 2015, including 5.6 million people in the World Health Organization European region, and over 2 million in the United States (US).[1, 2] In Africa, rates of HCV vary across countries, with the highest rates in Egypt, followed by Nigeria, and Ethiopia.[3] HCV is spread by exposure to blood including from unsafe injection practices. In addition, with an estimated 15.6 million people who inject drugs (PWID) worldwide, with over 25% of PWID aged 25 years or younger[4], injection drug use (IDU) is a major risk factor for HCV internationally. HCV can also be acquired from healthcare associated risk, such as from unscreened blood products or other healthcare associated exposures, with predominant risk factors varying by region. For example, in countries such as Egypt and Pakistan, nosocomial transmission continues to lead to high rates of HCV. Fortunately, the advent of direct acting antiviral (DAA) agents has dramatically shifted the landscape of HCV, allowing the treatment and cure of over 95% of individuals with access to treatment. However, there are significant global inequities in the access to diagnosis and treatment of hepatitis C. With around 90% of those with HCV residing in low- and middle-income countries, treatment coverage is less than 10% in most countries.[5]

There has been an increase in HCV among young adults related to IDU, including women of childbearing age and women who are being diagnosed during pregnancy, which has been well-described, particularly in the United States in parallel with the opioid epidemic. Given this shift in epidemiology, there has been an increased focus on addressing care pathways (including HCV screening during pregnancy), studying risks of HCV mother-to-child transmission, as well as beginning to investigate the role of antiviral therapy in the context of pregnancy. With the WHO plan for HCV elimination by the year 2030,[6] addressing HCV in women, and in particular during pregnancy, is imperative. For example, in the national response to the WHO goal, the Department of Health and Human Services National Viral Action Plan 2017-2020 specifically includes pregnant women as a priority population for HCV elimination due to the risk of perinatal HCV transmission.[7] Here we describe key considerations in addressing HCV in women during childbearing and during pregnancy.

Epidemiology of Hepatitis C in Women and During Pregnancy

Although there has been an increase in studies dedicated to understanding HCV burden in women and during pregnancy, many of the studies are U.S. based, and data on HCV burden in this important population across other health settings internationally is needed. As a result of the opioid epidemic, there has been an increase in HCV infection among women of childbearing age, as demonstrated in U.S. based studies. National commercial laboratory data in the U.S., from 2011 to 2016, demonstrated a significant increase in HCV testing among women of childbearing age (up by 39%), as well as an increase in the proportion who were HCV antibody (Ab) positive by 36% (from 4.4% to 6.0%), with the greatest increase occurring from 2015 to 2016.[8] Increases in HCV detection rates were also cited in women age 15-44 on a national level utilizing national Quest laboratory data from 2011-2014.[9] Similarly using the national notifiable disease surveillance system (NNDSS), a doubling of HCV diagnoses among women of childbearing age was seen from 2006 to 2014, with new infection diagnosed among women of childbearing age surpassing those among women in older age categories.[10] As a result, in the U.S., there has been a shift in HCV from a predominantly male disease to one that is largely equal between men and women. Outside of the U.S., countries with high prevalence of HCV,

such as Georgia, appear to have higher prevalence of diagnosed HCV among men than women, but trends over time have not been assessed,[11] and in many assessments, such as in Africa, women are often underrepresented in prevalence estimates.[3] Significant barriers to the prevention of HCV exist across geographical settings including low coverage of interventions to prevent the spread of HCV, inadequate policies to decrease risks for transmission, and barriers to medication access have made HCV elimination challenging to attain [4, 12] . Furthermore, in the setting of the recent COVID-19 pandemic, and concurrent increase in high risk drug use behaviors, as well as a disruption of worldwide hepatitis elimination programs, a further increase in HCV transmission among women at risk can be anticipated.[13], [14]

Rates of hepatitis C in women during pregnancy have also been evaluated through birth certificate data, national reporting systems and hospital-based assessments. A systematic review conducted of EU data, estimated prevalence of 0.1% to 0.9% in data from 2005-2015.[15] A meta-analysis was also conducted in Africa evaluating pregnancy prevalence estimates identifying a prevalence of 3.4% (95% CI: 2.6-4.2, 58 studies) from 2003 to 2015.[16] More recent studies with data from HCV prevalence in pregnancy are shown in **Table 1.** In a recent evaluation of all live births in the United States based on National Center for Health Statistics birth records, the rate of HCV infection among increased from 1.8 cases to 4.7 cases per 1000 live births.[17] Utilizing the Healthcare Cost and Utilization Project (HCUP) from 2000-2015 the CDC found that national rate of HCV infection among women giving birth increased over 400% from 0.8 to 4.1 per 1000 deliveries. Though rates were significantly higher among women with a history of opioid use disorder, increases were also seen in women without opioid use history.[18] Outside of the US, studies conducted in countries such as Poland (from 1998 to 2012), have also shown increased in hepatitis C prevalence diagnosed during pregnancy over time.[19] Like in the US, these increases are largely driven by increased HCV transmission due injection drug use, with increased prevalence of IDU over time among women who tested positive for HCV.[20]

It could also be argued that the increase in prevalence in this population is simply related to increased risk recognition and thus more testing. Nonetheless, testing for HCV during pregnancy is not uniform across practice settings potentially leading to significant underdiagnosis of HCV.[21] Changing and region specific epidemiology of HCV infection can be useful in determining strategies to guide risk reduction. In areas with high levels of maternal HCV infection, interventions such as implementation of a needle-exchange program (NEP), have shown promise in decreasing maternal HCV infection rates. For example, in 2011 in a town in Ohio with rapidly increasing rates of HCV infection, city officials declared a public health emergency and initiated a NEP funded by NGO donations. After its implementation the trajectory of maternal HCV significantly declined[22]

Evolving Screening recommendations for HCV during pregnancy

Although hepatitis C screening during pregnancy has traditionally been risk-based, rising rates of HCV and increased recognition of its implications on pregnancy have led to increased consideration for universal HCV screening, increasing opportunities for diagnosis of HCV and linkage to treatment. Currently, only a few countries recommend universal screening during pregnancy, including Italy, France, Poland, Taiwan, and Pakistan.[23-25] The cost of testing as well as the lack of access to treatment may explain the low uptake of HCV screening during pregnancy, particularly in low- and middle-income countries. In the U.S., a recent shift from risk-based to universal HCV screening was initially recommended by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in 2018,[26] citing increased prevalence of HCV among women and inefficacy of risk-based

screening. Subsequently, the United States Preventative Services Task Force (USPSTF) and the CDC both endorsed universal screening during pregnancy, with the CDC further recommending repeat screening at every pregnancy.[27, 28] These changes in national recommendations also came in response to cost-effectiveness studies demonstrating cost-effectiveness of universal screening (compare to risk-based screening) in the US (**Table 2**).[29, 30] However, at least in the U.S., the obstetric societies have not embraced universal screening yet.[31] Prior to increased uptake across health settings in the U.S., it will be necessary to have endorsement of universal screening by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM).[32] In addition, the question of when to re-screen after initial screening during pregnancy is an important one, and recent evaluation has demonstrated cost-effectiveness of rescreening in each subsequent pregnancy.[33] Internationally, the European Association for the Study of Liver Diseases (EASL)[34] and the Asian Pacific Association for the Study of the Liver (APASL)[35] both have recommended risk-based screening without updated recommendations for universal screening, and country-specific HCV prevalence and cost-effectiveness may guide future decisions regarding recommendations for universal screening.

Mother-to-child transmission of HCV

A major implication of diagnosing HCV during pregnancy is understanding the risk of mother-to-child transmission (MTCT). A 2014 meta-analysis of 109 studies of HCV-positive women from 1997 to 2012, estimated the MTCT rate as 5.8 % (95% CI, 4.2-7.8%), with transmission rates significantly higher among women who are HIV co-infected (10.8% (95% CI 7.6-15.2%).[36] Furthermore, much lower MTCT rates in observational studies of women coinfected with HIV on treatment have demonstrated that suppressive HIV therapy is a potentially successful intervention to decrease the risk of HCV transmission.[37-39] More recently, in a U.S. national cohort, a 3.6% rate of MTCT was identified[40] and in a recent study from Spain, an estimated 7% risk of transmission was noted among mothers coinfected with HIV.[41] However, given low rates of infant testing for MTCT and therefore limited data on true prevalence of HCV among infants born to mothers with HCV, an accurate estimate of the MTCT risk is challenging. For example, in a Philadelphia department of health study of 8119 females with HCV identified in a hepatitis registry, only 84 (16%) of their infants ever received HCV testing.[42] Similarly, in a population-based retrospective cohort of women in Pittsburgh, only 30% of at risk infants were tested for HCV.[43] In a prospective Egyptian study of 3000 pregnant women viral transmission was much higher than rates in the retrospective analysis. 46/3000 women were found to be HCV positive of which vertical transmission was identified in eight neonates (17.39%). High maternal viral load was identified as the only risk factor for transmission.[44]

Although it is thought that the majority of MTCT occurs perinatally, there is likely a small risk of earlier in utero transmission (**Figure 1**).[45] However, part of the challenge to understanding MTCT is the significant delay after birth to testing the infant for infection and then confirming viral infection. Current recommendations for assessment of MTCT is to test children for HCV Ab at ≥ 18 months of age, prior to which many may become lost to follow up[46] (**Figure 2**). Confirmation of chronic viremia may be postponed until after age 3 due to availability of treatment starting at age 3. This again may lead to a significant loss to follow up in children who test positive. Investigation of earlier testing strategies has demonstrated that infant testing for HCV-RNA PCR at age 2-6 months demonstrated high sensitivity and specificity for mother-to-child transmission as defined by positive HCV-RNA testing or anti-HCV at age ≥24 months and negative result as those that had negative anti-HCV at age ≥18 months.[40] Thus, consideration should be made towards implementing revised criteria for evaluation of MTCT at an earlier

infant age, as this will certainly increase the number of infants appropriately tested and diagnosed.

Pregnancy-related risk factors for MTCT have also been evaluated. In a systematic review of eighteen observational studies addressing MTCT, there was no clear association seen between mode of delivery (vaginal versus cesarean) and risk of transmission, nor was an association seen between breastfeeding and risk for transmission (**Table 3**).[47] Although two studies included in the systematic review reported an association between prolonged duration of ruptured membranes and risk of transmission,[47] based on these findings there are limited pregnancy management interventions that can be done to decrease risk of transmission. Although avoidance of certain obstetric procedures, such as amniotomy and invasive fetal monitoring, may decrease perinatal HCV transmission, evidence is lacking.[48] Furthermore, although it has been proposed that higher HCV viral load may be associated with increased risk of MTCT, a viral load threshold for increased transmission has not been defined and interventions to reduce risk cannot be recommended based on viral load.[49]

Implications of HCV on pregnancy outcomes

Infection with HCV during pregnancy has been associated with adverse pregnancy outcomes, as seen predominantly in large retrospective studies. In a large meta-analysis of over 4 million women with over 5000 HCV infected women, there was a significant association seen with preterm birth in women with HCV (OR 1.62 (95% CI 1.48-1.76), including after stratification for other key contributors to adverse pregnancy outcomes including smoking/ alcohol abuse, maternal drug abuse, or coinfection with HBV or HIV. [50] Similarly a Swedish registry with over 2000 HCV births saw an association of HCV with preterm birth (aRR 1.32 (95% CI 1.08-1.60) and late neonatal death (aRR 3.79 (95% CI 1.07-13.79) when adjusting for maternal age, smoking, BMI, diabetes, and alcohol use. [51] Perhaps the most established association of adverse pregnancy outcome with HCV is with intrahepatic cholestasis of pregnancy (ICP), with significantly higher risk of developing ICP (OR 5.76; 95% CI 1.30-25.44) in women with pre-pregnancy hepatitis C, and a pooled OR as high as 20.40 (95% CI 9.29-44.33) for ICP in HCV-infected pregnant women compared to non-HCV pregnant women.[52, 53] Given this significant increase in risk, and the known association of ICP with adverse fetal outcomes,[54] women with HCV should be counseled on this potential risk during prenatal counseling. On the other hand, it is currently not known whether HCV treatment or clearance during pregnancy would decrease the risk of ICP, or other adverse pregnancy outcomes.

Considerations for DAA therapy in the pregnancy care context

Given the increased risk of adverse pregnancy outcomes associated with HCV during pregnancy, perinatal transmiaaion,as well as increased rates of HCV diagnosis during pregnancy,[17] the question of optimal HCV treatment timing in relation to pregnancy is being evaluated (**Figure 3**). Although previously AASLD/ IDSA guidelines recommended to strictly avoid treatment during pregnancy, current recommendations are that “treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits.”[55] Although ideally women should be treated prior to pregnancy, if diagnosed with HCV during pregnancy, counseling should be aimed at determining when HCV treatment would be possible. Furthermore, when women with a history of HCV seeking care at a tertiary care center in the U.S. (study conducted at University of California San Francisco liver diseases clinic) were surveyed about *their* preferences and views

toward treatment during pregnancy, more than half stated that they would consider DAA therapy during pregnancy if it were to prevent MTCT.[56]

Safety in this population is paramount. Although real world exposure data is limited, animal reproduction studies have demonstrated DAA safety with no evidence of adverse developmental outcomes observed with sofosbuvir based therapies or glecaprevir/pibrentasvir (GP). In animal based studies, exposures to the predominant circulating metabolite of sofosbuvir (GS-331007) were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the recommended human dose.[57] Similarly, in animal reproduction studies, no adverse developmental effects were observed when the components of GP were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) the human exposures at the recommended dose.[58] Furthermore, prior human safety evaluations have found DAAs safe, but therapy to effectively prevent MTCT has not been established. [59]

Given reassuring animal safety data, investigation into potential treatment with DAAs during pregnancy or soon after delivery are underway. Most recently, the first trial of HCV treatment during pregnancy has been conducted in a single-center study in Pittsburgh enrolling 9 patients during second and third trimesters of pregnancy for treatment with sofosbuvir/ ledipasvir for a 12-week treatment duration, and finding that HCV treatment during pregnancy was safe, effective, and well-tolerated. [60] However, recruitment into the trial was limited by participation, retention in the study (one patient did not complete all assessments needed), as well as exclusion of genotype 3 infected women. Ongoing studies include assessment of postpartum treatment with the use of sofosbuvir/ velpatasvir in women enrolled in an observational study in Ohio who are offered treatment after cessation of breastfeeding as well as a single arm Phase 1 Pharmacokinetic Trial of Sofosbuvir/Velpatasvir investigating the use of sofosbuvir/ velpatasvir during pregnancy.[61],[62]

Many providers are hesitant to consider DAA treatment without sufficient safety data, and larger scale studies may be needed to establish safety and efficacy of treatment with DAAs during pregnancy. Although we know that highest rates of potential teratogenicity occur during first trimester with drug exposure, safety established during 3rd trimester of treatment (and potentially breastfeeding) will be necessary. Furthermore, models of care with linkage to treatment prior to conception and after delivery/ breastfeeding are needed. Guidelines now suggest that treatment during pregnancy is a risk/benefit conversation between woman and provider, but until women are accepting of treatment this opportunity for cure (and decreased vertical/hortizontal transmission) will be lost. Demonstrating safety is only one component. Assuring women that DAA therapy during pregnancy is important for their health and the health of their unborn child will require not just patient buy in but also provider buy in. Given that obstetric guidelines don't yet advocate for universal screening in pregnancy, convincing this group of providers to navigate a care cascade will continue to be a lost opportunity.

Conclusions

The epidemiology of HCV has shifted over the last decade as a result of the opioid epidemic in the U.S. as well as injection drug use as well as healthcare associated exposures in other regions of the world, leading to the recognition of more women of childbearing age being infected with HCV as well as higher rates of HCV diagnosis during pregnancy. Although in a few regions a clear shift in guideline recommendation has been made to endorse universal HCV screening in pregnancy, it is yet to be determined whether these recommendations will be made more broadly internationally, and whether it will lead to a significant increase in HCV diagnosed during pregnancy. Regardless, it will be important to improve our understanding of the implications of having HCV during pregnancy, as well as role for HCV treatment in the

pregnancy context. Future directions should also involve evaluating cost-effectiveness, feasibility, and effectiveness of DAA treatment during pregnancy, as well as developing models of care to optimally reduce the risk of MTCT.

Tables/ Figures:

Table 1. Recent international Studies addressing estimates of HCV during pregnancy (published 2019 – present)

Author, Year	Country	Study Design, Recruiting period	Sample Size	HCV Prevalence Estimate	HCV viremia present?	Risk factor profiles
	Europe					
Piffer et al. (2020)	Italy	Retrospective observational; Trento Provence; 2009-2018	45493	3.9% (95% CI 3.8, 4.0)	N/A	1% HIV positive; 18% IDU
Millbourn et al. (2020)	Sweden	Prospective HCV screening; 2013-2016	4108	0.7% (95% CI 0.3, 0.7)	0.4% (95% CI 0.3, 0.7) viremic	80% drug use
Ruiz-Extremera A et al. (2020)	Spain	Multicenter Open-Cohort; 2015	7659	0.26%	40% viremic among HCV Ab positive	45% IDU; 10% HIV
Tanriverdi E et al. (2019)	Turkey	Hospital-based; 2013-2016	9709	0.06%	N/A	0% HIV;
	Asia					
Mostafa A et al. (2020)	Egypt	Hospital-based; 2018	2177	0.9%	87% viremic among HCV Ab positive	0% HIV; Blood transfusion and age≥30 were risk factors
	North America					

Rossi R, et al. (2020)	United States	National Center for Health Statistics Birth Records; 2014-2017	31207898	0.30% (increase from 1.8 to 4.7/ 1000 live births)	N/A	Non-hispanic white race, Medicaid insurance, cigarette smoking associated with HCV
Prasad M et al. (2020)	United States	Maternal fetal medicine unit network	106842	2.4 cases (95% CI 2.1-2.7) per 1000	35% of positive HCV Ab viremic	53% IDU; 0% HIV
Africa						
Frempong, et al. (2020)	Ghana	Cross-sectional; 2012-2013	248	7%	N/A	33% HIV positive
. Ifeorah I, et al. (2020)	Nigeria	Regional in Kogi State;	176	4.6%	2.2% viremia	0% HIV; 0% IDU; 4.5% piercing; 6% history of surgery
Chibwe E, et al. (2019)	Tanzania	Cross-sectional; 2017	339	0.03% (95% CI 0.1-0.4%)	N/A	N/A
Oluremi A, et al. (2020)	Nigeria	Hospital-based; 2019	904	0.8%	Not tested	N/A
Omatola C, et al. (2019)	Nigeria	Hospital based; 2017	200	2.6% (2.32-2.87)	N/A	0% IDU
Latin America						
Vargas et al. (2020)	Salvador, Brazil	Cross-sectional; 2016-2017	2099	0.1%	0.1% viremic; 0.3% non-viremic	NA

Table 2. Cost-effectiveness studies of universal HCV screening during pregnancy in DAA era

Study	Assumptions	ICER	Cost-effective?
Chaillon et al. (2019)	HCV prevalence 0.73%	<$3000	Yes (if HCV prevalence > 0.07%)
Tasilo et al. (2019)	Time to cirrhosis < 70 years; HCV prevalence > 0.16%	$41000	Yes
Selvapatt N et al. (2015)	HCV prevalence 0.38%	£2400	Yes

Table 3. Factors during pregnancy and breastfeeding that have been evaluated in regards to MTCT (adapted from Cottrell, et al. 2013)[47]

Variable	Studies; # women	Precision of Evidence	Summary of findings
Elective C/S vs. vaginal delivery	4 cohort studies; N=2080	Low	No differences, but trends in opposite directions in highest quality studies
All C/S vs. vaginal delivery	11 cohort studies; N=2308	Low	No association
Invasive fetal monitoring vs. none	3 cohort studies; N=928	Low	Inconsistent but one good quality study OR=6.7 (95% CI 1.1-36)
Prolonged rupture of membranes vs. no	2 cohort studies; N=245	Low	Yes with > 6 hours having OR=9.3 (95% CI 1.5-18)

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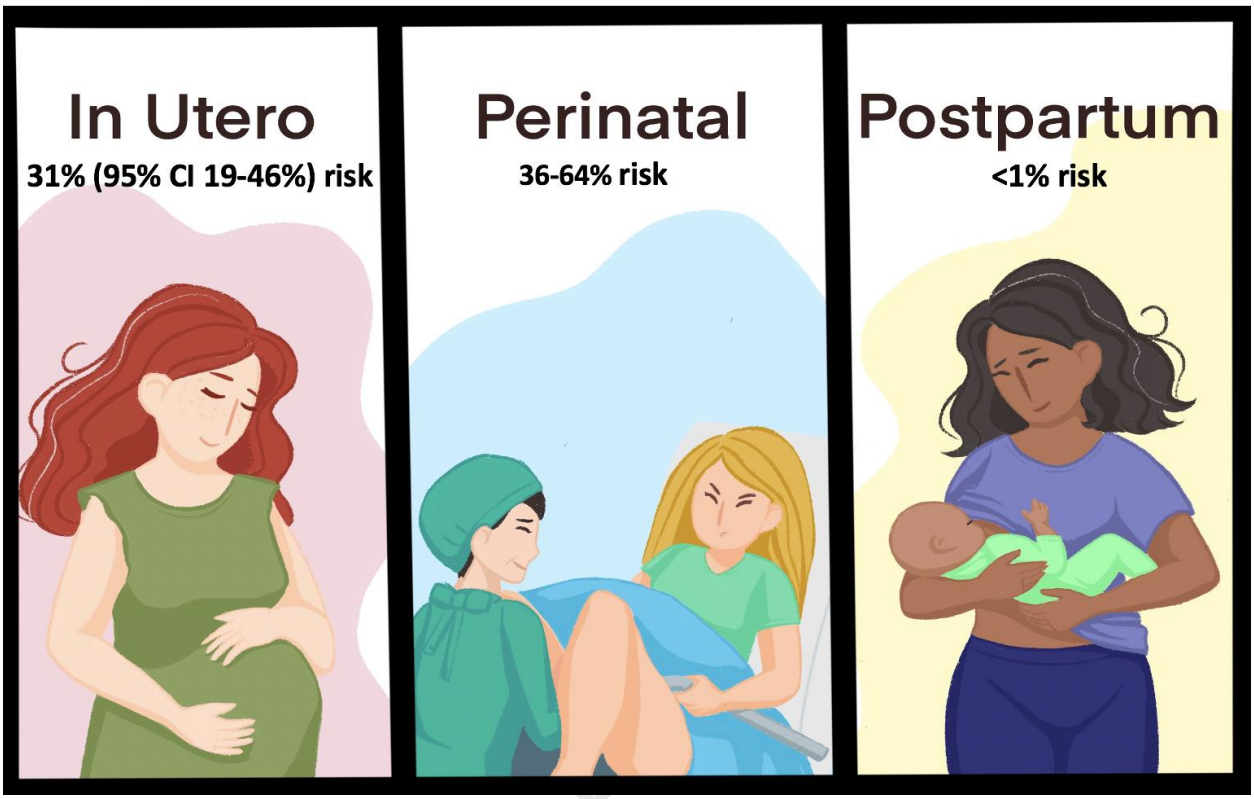
Figure 1: Timing for mother-to-child transmission of HCV



Maternal to Child Transmission of HCV can occur during pregnancy (in utero) but is more commonly thought to occur in the peri-partum time period (Mok et al. 2005),

Figure 2: Assessment of mother-to-child transmission and potential pediatric treatment initiation

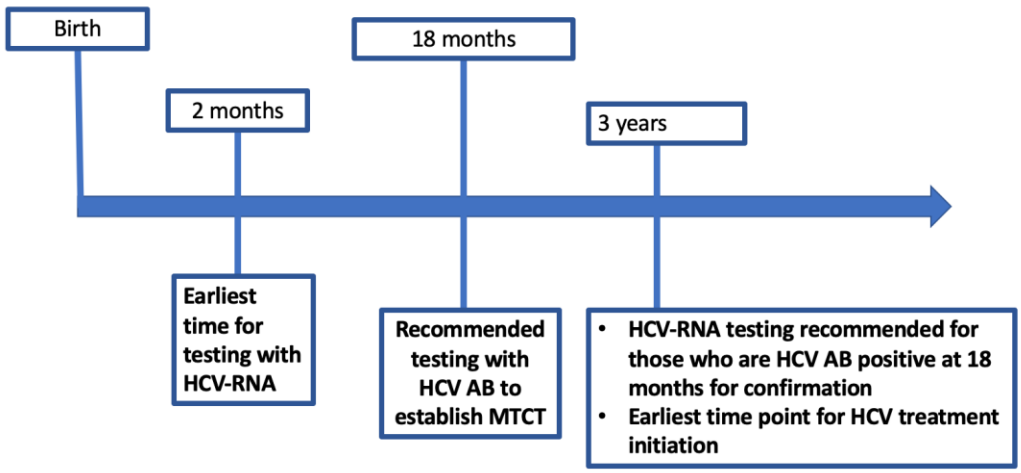


Figure 3: Pros and Cons of HCV treatment during pregnancy and breastfeeding

TREATMENT WITH DAAS DURING PREGNANCY AND BREASTFEEDING

1. Maternal cure while engaged in pregnancy care
2. Possible decrease in MTCT
3. Maternal treatment while under insurance coverage
4. Decrease in community transmission
5. Potential decrease in HCV-associated adverse pregnancy outcomes?

1. Human safety in pregnancy not established
2. Safety during breastfeeding not established
3. More established data for treatment prior to pregnancy or children starting at age 3
4. Difficulty in accessing DAA therapy in time (prior to delivery)
5. Cost-effectiveness not established

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