MOTHER TO CHILD TRANSMISSION OF HEPATITIS C VIRUS

Screening management and current recommendations

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Overview of HCV infection and vertical transmission

Globally more than 184 million[1] people have chronic HCV infection. Vaccinations do not exist against HCV; therefore, primary prevention measures remain essential, particularly for vulnerable populations and newborns. HCV seroprevalence among the Canadian general population is relatively low, and the highest prevalence 1.55% [95%CI; 1.32, 1.81] is reported to be in the adult cohort born between 1945 and 1974 in the province of Ontario[2]. New incidence rate of Hepatitis C are being reported consistently above the national average between 2006 and 2015 in Ontario[3].

KEY CONCEPTS

- HCV screening for vulnerable pregnant women and their newborns is recommended. Vertical transmission occurs in at least 1 in 20 of children born to HCV positive mothers (doubled if co-infected with HIV).
- Poor pregnancy outcomes including preterm birth, are reported in HCV positive mothers, and treatment during pregnancy may become available in the near future. Current guidelines strongly recommends HCV eradication prior to conception, however evidence remain uncertain for treatment during pregnancy.
- Risk factors for HCV vertical transmission include HIV co-infection and possibly mothers with high HCV viral load and exposure to maternal blood during vaginal delivery.
- Elective C-section does not reduce HCV vertical transmission and is not recommended unless otherwise indicated. Evidence lacks on determining effects of other delivery related procedures including internal fetal monitoring and amniocentesis.
- HCV RNA test is recommended for 2nd and 4th months of life, and Anti-HCV antibody test is recommended after 18 months for infants born to HCV positive mothers.
- Two positive HCV RNA tests in early months of life or a positive Anti-HCV test at 18 months, aided by HCV RNA testing indicates vertically transmitted HCV in infants.
- Breastfeeding is safe for HCV positive mothers, unless co-infected with HIV or cracked nipples.

HCV vertical transmission is commonly defined as infection received within first 28 days[4] of life from mother, although US CDC extended perinatal HCV infection up to 36 months[5]. Rate for vertical transmission in HIV-negative mothers is approximately 5.8% [95%CI; 4.2, 7.8], and 10.8% [95%CI; 7.6, 15.2] for HIV-positive mothers[6]. Vertical transmission occurs intrauterine, peripartum and postpartum periods; occurrence is most common during peripartum[6,7]. Intrauterine mechanisms involve viral particles transcytosis, infected peripheral mononuclear cells, and trophoblasts infection in placenta[6,8,9]. Risk based selective screening for prenatal care is practiced in low prevalence countries including the USA [10,11] and Canada. Universal HCV screening for pregnant women is commonly reported in high endemic countries including Egypt[12] and Mongolia. Screening for HCV among vulnerable population including injection drug users and recent immigrants from endemic countries is essential, particularly for women of reproductive age.

Treatment options during pregnancy for HCV eradication and pregnancy outcomes

Previous "pegylated interferon and ribavirin" combinations were contraindicated during pregnancy due to low tolerability and possible teratogenic effects[13]. Following the discovery of four class direct acting antivirals (DAAs), HCV eradication became more efficient and highly tolerable, with over 90% sustained virologic response rate. Numerous DAAs provide low toxicity level during pregnancy, yet clinical trials remain

lacking. Currently only 2 clinical trials (SOF/VEL[14] and LDV/SOF[15]) have been registered at clinicaltrials.gov for pregnant women, and no clinical trials are published for pregnant women. Viral eradication therapy is strongly recommended ideally prior to conception[16,17]. However, clinical trials and combination therapies should not be discouraged for reducing poor pregnancy outcomes including preterm birth[18], intrahepatic cholestasis[19], low birth weight[20,21], gestational diabetes mellitus[21] and to prevent vertical transmission. HCV genotype distribution is heterogenous in Canada which determines the treatment; 1a (48%), 1b (19%), 2a (6%), 2b (3%), 3a (22%), and 4a (1%), respectively[22]. Treatment options and teratogenic profile is shown in the supplementary Table 1. Currently no evidence exists on Hepatitis C viral eradication treatment during pregnancy, however many guidelines strongly recommend the treatment for reproductive age prior conception.

Risk factors associated with vertical transmission

HIV Co-infection is a well-established risk factor of HCV vertical transmission, with transmission rates 2.82 fold higher than HIV-negative mothers[23,24]. High viral load of HCV in pregnant mothers is associated with increased risk of vertical transmission [25,26], however systematic review and meta-analysis is lacking. HIV co-infection and high HCV viral loads are classified as intrauterine transmission risk factors that contribute to at least one third of the vertical transmission[27] along with other intrauterine transmission risk factors. Risk factors associated with peripartum period transmission including delivery route, internal fetal monitoring, prolonged rupture of membrane and amniocentesis are less understood and results are not conclusive to provide clear clinical guidance[25,27,28]. Elective C-Section has not been shown to reduce the risk of HCV vertical transmission[29]. Breastfeeding is not associated with vertical transmission of HCV [30]. Summary of HCV vertical transmission risk factors is given in Table 2, and risk factors other than HIV co-infection requires stronger evidence and future investigations.

Current recommendations for testing in children born to HCV positive mothers

Although numerous committees and government bodies have published recommendations for HCV screening for high risk newborns, well-recognized and globally acceptable consensus is lacking[31-37]. The HCV RNA test remains acceptable as an initial test for newborns within first year of life, due to Anti-HCV antibodies being passively transferred from mothers without the viral infection[25,36,38,39]. In majority of HCV negative infants, maternal Anti-HCV antibodies become undetectable at 18 months (Figure 1)[25,38,39]. An Anti-HCV antibody test is acceptable from 18 months of life in most guidelines as initial screening[33,35,37]. Overall, infants who are positive for HCV RNA on two separate occasions in early months of life or Anti-HCV positive after 18 months confirmed by HCV RNA or HCV Core antigen test are identified as vertically transmitted HCV[17,32-37]. However Public Health Ontario recommends HCV RNA test at 2nd and 4th months of life for infants born to HCV positive mothers[31]. Detailed review for various guidelines and testing methods can be found in Table 3 and 4 in the supplement section [17,32-37]. HCV RNA test would identify actively replicating infection and alternatively with HCV Core antigen test.

Beyond detection and childhood management

Breastfeeding is promoted except HIV co-infected mothers and during maternal blood exposure conditions, particularly cracked nipples [17,31,34]. Human breast milk has been shown to have antiviral activities for HCV[40], and breastfeeding is relatively safe for HIV negative mothers[30]. Although severe progression of HCV related liver disorder is relatively rare in children, viral eradication is available for children after 12 years of age, and DAAs may become available for children as young as 3 years old[17]. In a study with mostly vertically transmitted children participants, HCV spontaneous clearance occurred for 9%[41] of the cohort and other studies report up to 28%[42] spontaneous clearance in children. Viral eradication treatment during childhood may become more common in near future, and pediatric HCV eradication aligns with Canadian Hepatitis C elimination efforts and policy.

Supplements

Table 1. Comparison of eradication therapy combinations and pregnancy category

Combination name and duration of treatment	Recommended HCV Genotypes [17]	Teratogenic classification [43]	ODB coverage[44] / Health Insurance Mongolia coverage[45]
Ledipasvir 90 mg + Sofosbuvir 400 mg / 12 weeks	1a, 1b	B1	Limited use / Not covered**
Glecaprevir 300 mg + Pibrentasvir 120 mg / 8 weeks*	1a, 1b, 2, 3, 4	B1	Limited use / Not covered
Sofosbuvir 400 mg + Velpatasvir 100 mg 12 weeks	1a, 1b, 2, 3, 4	B1	Limited use / Not covered

*- 3 tablets daily formula, **- Special market price apply

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Table 2. Risk factors associated with HCV vertical transmission

Author and year	Independent variable and analysis type	Effect size and total number of mother child pairs	Interpretation and Remarks
Pappalardo BL / 2003 [23]	HIV Co-infection / systematic review and meta-analysis	2.82 [95% CI: 1.78-4.45; p = 0.00001] / 2382	HIV co-infected mothers have 2.82 times likely to vertically transmit HCV than HCV mono-infected mothers
Polis CB et al / 2007 [24]	HIV Co-infection / systematic review and meta-analysis	2.82 [95% CI: 1.17-6.81; p = 0.011] / 4424	Only HCV Viremia studies were included for meta-analysis
Murakami J et al / 2012 [26]	HCV Viral load > $6.0 * 10^5$ IU/ml / prospective design	10 in 34 VS 0 in 41 (Fischer's exact test, p<0.001) / 188	Maternal HCV high viral load is associated with increased vertical transmission
Ghamar Chehreh ME et al / 2011 [29]	Elective C-section / systematic review and meta-analysis	1.1 [95% CI: 0.45-2.67; p = 0.35] / 641	C-section does not reduce HCV vertical transmission
Eric M et al / 2005 [25]	Prolonged rupture of membrane > 6h / prospective cohort	9.3 [95% CI: 1.5-179.7] / 244	adjusted OR for p<0.1 factors
Eric M et al / 2005 [25]	Internal fetal monitoring / prospective cohort	6.7 [95% CI: 1.1– 35.9] / 244	adjusted OR for p<0.1 factors
Gagnon A et al / 2014 [28]	Amniocentesis / systematic review	N/A	Not associated with vertical transmission and weak evidence
Bhola K and McGuire W / 2007 [30]	Avoidance of breast feeding / systematic review	N/A / 1854	Breastfeeding is not associated with HCV vertical transmission

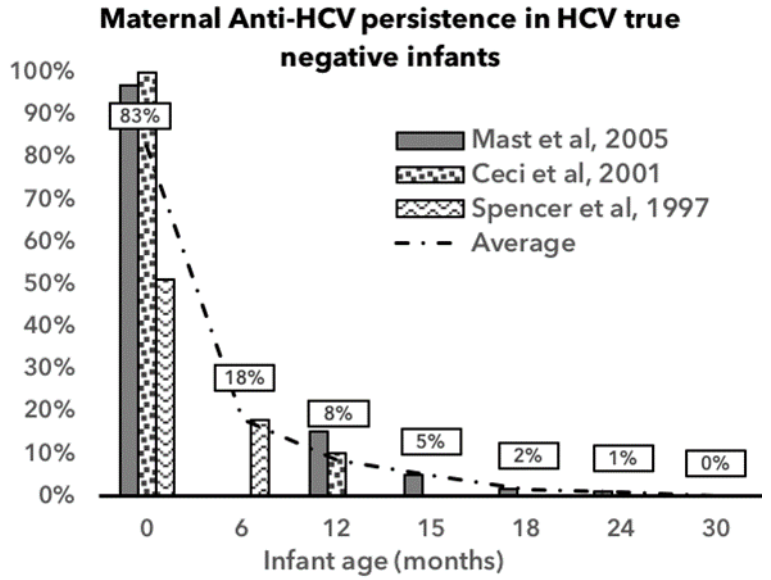

Figure 1. Serological findings of HCV never exposed infants born to HCV positive mothers

Table 3. Various HCV testing recommendations for infants born to infected mothers

Country, year / Organization	First test and onset	Follow up test	Role of Anti-HCV	Remarks
Canada 2015 / Ontario Public Health[31]	HCV RNA at 2 and 4 months	HCV RNA and Anti-HCV at 18 and 24 months	Confirmatory	Contains comprehensive strong review materials
USA 2019 (reviewed) / CDC[34]	Anti-HCV at 18 months *(HCV RNA at 1-2 months per request)*	Subsequent HCV RNA test, separate visit	Initial screening	Unique case definition system
Canada 2014 / Manitoba Public Health Branch [33]	Anti-HCV at 12-18 months *(HCV RNA at 2 months per request)*	Anti-HCV at 18 months	Both initial and confirmatory	Negative RNA test should be confirmed by Anti-HCV test to rule out false negative
Australia 2017 / North Metropolitan Health Service[35]	Anti-HCV at 18 months *(HCV RNA at 2-6 months per request)*	N/A (HCV RNA after 3-4 months)	Initial screening	Perinatal infection is used for definition
Canada 2016 / BC Centre for Disease Control[36]	HCV RNA at 4-6 weeks	Anti-HCV at 18 months	Confirmatory	Maternal Anti-HCV remain 18 months, 95% cleared by 12 months
UK 2018 / Norfolk and Norwich University Hospitals [32]	HCV RNA at 2-3 months	HCV RNA at 8-12 months	Confirmatory	NAAT positive cases are managed by specialists
New Zealand 2015 / Auckland District Health Board[37]	Anti-HCV at 15 months *(HCV RNA at 4-6 months per request only)*	HCV RNA and LFT for first test positive	Initial screening	Discourages use of cord blood testing

Table 4. Characteristics of HCV detection assays[16]

Test type	Assay principle	Sensitivity and Specificity	Interpretation
Anti-HCV *	Rapid diagnostic test - Enzyme immunoassay	98% [95% CI: 98%-100%] and 100% [95% CI: 100%-100%] [10]	Widely used for screening purposes, one forth positive case spontaneously resolve, identifies previous exposure.
HCV RNA **	Reverse transcriptase - Polymerase chain reaction	81% [95% CI: 58%–95] and 93% [95% CI: 85%–98%] [46]	Highly sensitive and specific, indicates viral replication in both acute and chronic infections.
HCV core antigen *	Chemiluminescent assay	93.94% [95% CI: 93.73%–94.15%] and 96.63% [95% CI: 96.42%–96.85%] [47]	Serum or plasma sample based cost-effective alternative to HCV RNA test. Less sensitive than RNA test, indicates active viral replication.

*- HCV RNA test as golden standard, **- between 2 and 6 months of age

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