Research Article
Viral Hepatitis

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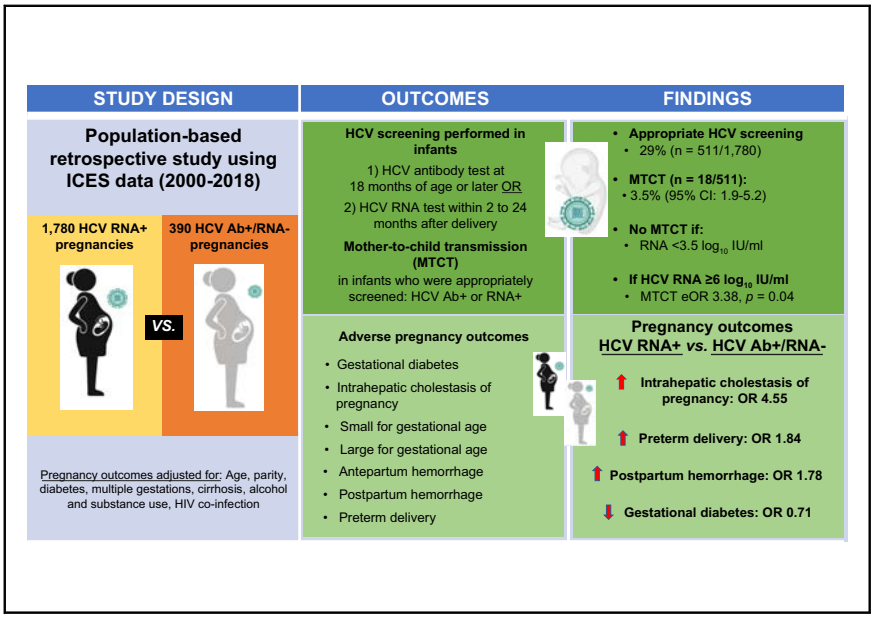
Influence of hepatitis C viral parameters on pregnancy complications and risk of mother-to-child transmission

Graphical abstract



Highlights

- HCV viremia was associated with adverse pregnancy outcomes including intrahepatic cholestasis of pregnancy and postpartum hemorrhage.
- Few infants received appropriate testing for perinatal transmission.
- Mother-to-child transmission of hepatitis C was estimated to be 3.5% among those infants tested.
- HCV RNA ≥6.0 $\log_{10}$ IU/ml was significantly associated with mother-to-child transmission.

Authors

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Lay summary

The prevalence of hepatitis C has increased in women of childbearing age and has important implications for women who become pregnant and their infants. We evaluated the effect that hepatitis C has on pregnancy outcomes as well as the rate of hepatitis C transmission to infants in a large database with linked mother-infant records. We found that active hepatitis C during pregnancy increased the risk of pregnancy complications. We also identified very low rates of testing of infants born to mothers with hepatitis C, but found higher rates of hepatitis C transmission to infants in mothers with higher virus levels.

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Influence of hepatitis C viral parameters on pregnancy complications and risk of mother-to-child transmission

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Background & Aims: With the World Health Organization plan for hepatitis C elimination by the year 2030, and recent guideline recommendations to screen all women during pregnancy for HCV, data on HCV in pregnancy are needed to determine the association of HCV viremia with adverse pregnancy outcomes and mother-to-child transmission (MTCT).

Methods: This retrospective cohort study was performed in Ontario, Canada, using population-based administrative healthcare data. Individuals were stratified based on whether they had active HCV viremia during pregnancy or resolved viremia at time of pregnancy. Peak HCV viral load was determined. Logistic regression was used to determine the association of viremia with adverse pregnancy outcomes; maternal HCV RNA levels were evaluated as a predictor of MTCT.

Results: We identified a total of 2,170 pregnancies in 1,636 women who were HCV RNA positive prior to pregnancy; 1,780 (82%) pregnancies occurred in women who were HCV RNA positive during pregnancy. Patients who were HCV RNA positive during pregnancy were more likely to have preterm delivery (18% *vs.* 12%, $p = 0.002$), intrahepatic cholestasis of pregnancy (4% *vs.* <2%, $p = 0.003$), and post-partum hemorrhage (9% *vs.* 5%, $p = 0.013$), and less likely to have gestational diabetes (6% *vs.* 10%, $p = 0.008$) than those with resolved infection. Only 511 (29%) infants had screening consistent with guidelines after birth; there was an estimated 3.5% risk of MTCT. HCV RNA ≥6.0 $\log_{10}$ IU/ml was significantly associated with MTCT (exact odds ratio 3.4, $p = 0.04$).

Conclusion: Active HCV viremia among individuals with a history of HCV infection significantly increases adverse pregnancy outcomes. Few infants are screened for MTCT. Higher HCV RNA is associated with increased risk of MTCT.

Lay summary: The prevalence of hepatitis C has increased in women of child-bearing age and has important implications for women who become pregnant and their infants. We evaluated the effect that hepatitis C has on pregnancy outcomes as well as the rate of hepatitis C transmission to infants in a large database with linked mother-infant records. We found that active hepatitis C during pregnancy increased the risk of pregnancy complications. We also identified very low rates of testing of infants born to mothers with hepatitis C, but found higher rates of hepatitis C transmission to infants in mothers with higher virus levels.

Introduction

HCV is a major public health concern affecting an estimated 15 million women of child-bearing potential[1] and 3.3 million children worldwide.[2,3] Over the past decade, as a result of the opioid epidemic, there has been an increase in the incidence and the prevalence of HCV among women of child-bearing potential as well as an increase in HCV detected during pregnancy.[4–7] Given these increases, the United States CDC, the United States Preventive Services Task Force, the American Association for the Study of Liver diseases and the Infectious Disease Society of America, and most recently the American College of Obstetricians and Gynecologists have recommended HCV screening in all pregnant women, regardless of the presence of risk factors for HCV.[8–11] To achieve the World Health Organization (WHO) goals to eliminate HCV as a public health threat by 2030, screening during pregnancy will be an important opportunity to identify and engage women in care, as well as to ensure infants born to mothers with HCV are being screened.

To date there are no specific interventions during pregnancy to decrease the rate of mother-to-child transmission (MTCT), only procedures to avoid that are associated with increased risk.[12] Historic data suggest that in HCV-monoinfected women the risk of MTCT is ~6%[13] yet more recent data indicate rates may be as high as 13%.[14] However, whether a specific HCV viral load threshold is associated with a heightened risk of MTCT, as has been shown in pregnant women with HBV, has not been well studied. Additionally, prior studies have suggested that women with HCV in pregnancy have increased risk of multiple adverse pregnancy outcomes compared to women never infected with HCV, including cholestasis of pregnancy, gestational diabetes,

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growth restriction, and preterm birth.[15,16] Yet it remains unclear whether these associations are due to HCV viremia itself or are subject to residual confounding by factors more prevalent among HCV-positive women, such as sociodemographic factors, substance misuse and co-morbid illness.[15–18] In order to advance our understanding of the impact of HCV on pregnancy and to facilitate counselling and management of this population, we utilized a large contemporary population-level database with linked maternal-infant data to evaluate the association between HCV viral parameters and MTCT and adverse pregnancy outcomes.

Patients and methods

Study design and database

This study was a population-based retrospective cohort study using data routinely collected under universal healthcare coverage in Ontario, Canada and housed at the ICES administrative data repository from January 2000 to December 2018. ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. Ontario provides universal healthcare coverage for its population of approximately 14 million individuals through the Ontario Health Insurance Program (OHIP). The population of Ontario is ethnically diverse, with 25% belonging to a visible minority and 2% being of Indigenous descent.

Details regarding all databases used in this study are outlined in Table S1. The primary databases used to define the cohort were the MOMBABY dataset (routine mother-infant linkage data), and lab data from Public Health Ontario (PHO) and the Ontario Laboratory Information Systems (OLIS). The other databases used to define the study variables included: the Registered Persons Database (RPDB – demographic information), The Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD – inpatient data), the National Ambulatory Care Reporting System (NACRS – emergency room data), the OHIP Physician Claims Database (outpatient data), the Ontario Drug Benefit (ODB) Claims Database (antiviral therapy claims), the ICES Physician Database, and the Postal Code Conversion File (PCCF – geographical area level data). All databases were linked at the individual-level and analyzed at ICES-Queen's. This study was approved by the Health Sciences Research Ethics Board at Queen's University (DMED 2352-20).

Cohort definition and follow-up

All pregnancies in women aged 15-55 from January 2000 to December 2016 were included if the mother had at least 1 positive HCV RNA test result prior to the date of delivery. Although we acknowledge some pregnant individuals do not identify as women, because gender is not captured in the database, we have used "women" throughout the manuscript. In women who had more than 1 pregnancy after a positive HCV RNA test, each pregnancy was evaluated separately. Women were excluded if they lacked a unique identifier and had less than 2 years of OHIP eligibility prior to their estimated date of conception (Fig. 1). All mother-infant pairs were followed for

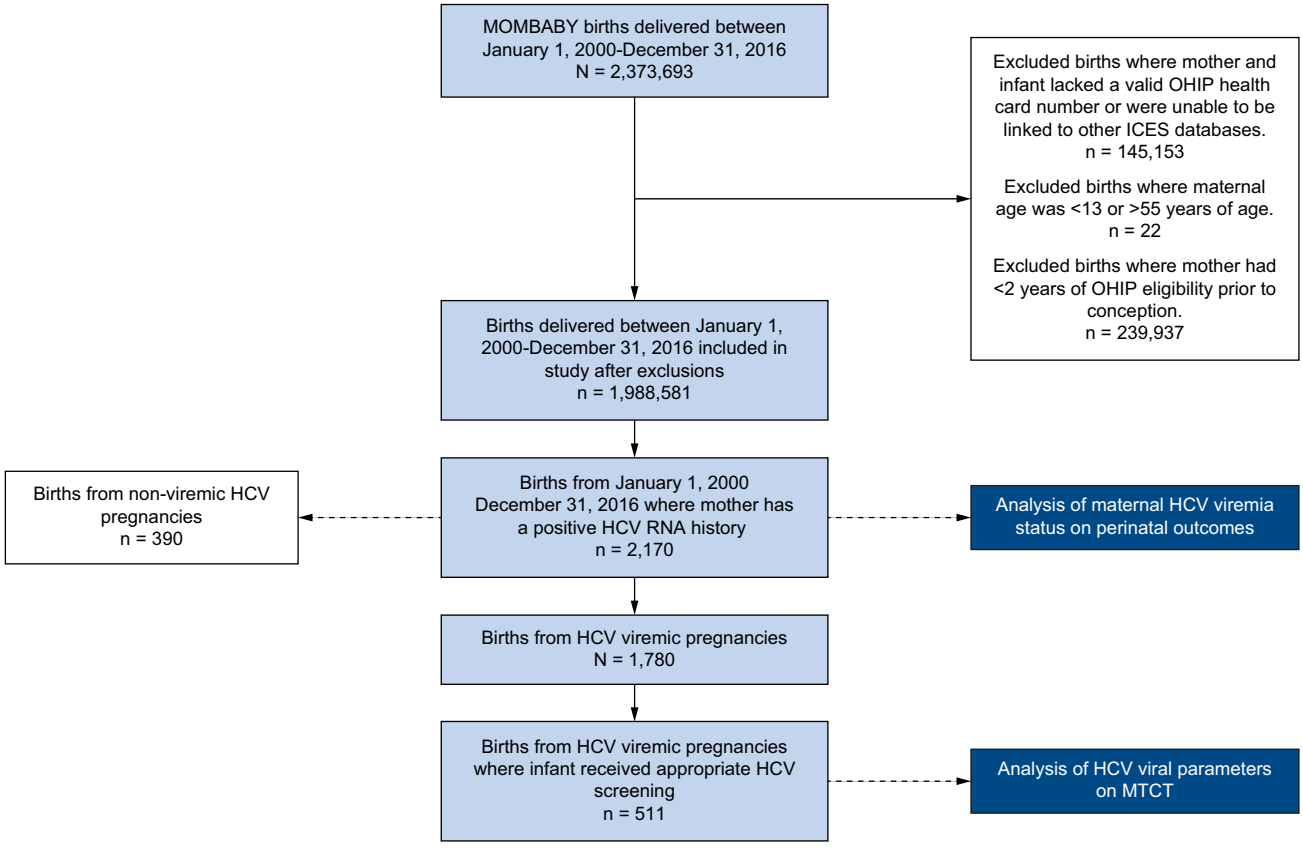

Fig. 1. Flowchart outlining creation of study cohorts for HCV viremic pregnancies.

perinatal outcome events up to 6-weeks post-partum and for MTCT until December 31, 2018. Mothers and infants were censored at the time of loss of OHIP coverage or death.

A cohort of all pregnancies in women aged 15-55 *without* evidence of HCV (based on viral serology results and administrative coding for viral hepatitis) was also identified from the MOMBABY database and was used to compare perinatal outcomes between women with and without a history of HCV.

HCV test results

HCV viral parameters were obtained from both PHO and OLIS data. PHO performs all HCV RNA testing in the province of Ontario; we captured HCV RNA results for all pregnant individuals included in our cohort. While some HCV antibody (Ab) testing is completed through PHO, private laboratories and some hospitals also have the capacity to perform HCV Ab testing which can be identified in OLIS data – we captured HCV Ab testing if available for infants born to mothers with HCV included in our cohort. Other HCV tests captured included HCV RNA viral load and HCV genotype. Although most HCV RNA results included a quantitative RNA value, prior to 2008, some RNA results were expressed as a qualitative result only. If HCV RNA was positive during pregnancy, the trimester of the most recent positive result was described. If the last positive RNA result was prior to conception, the time from last positive test to conception was calculated.

Demographics and co-variates

A summary of the study variables used are outlined in Table S2. Maternal age at the time of delivery and infant age at the time of HCV testing were determined from the date of birth in the RPDB. Socioeconomic status and urban or rural location were defined using PCCF to link postal codes in the RPDB to income quintiles from Statistics Canada. Parity (nulliparous *vs.* parous) was defined based on linkage to the MOMBABY dataset. Co-morbid illness was defined using the Elixhauser co-morbidity index[19] using a 2-year lookback for inpatient hospital diagnoses. The presence of pre-conception diabetes, hypertension, HIV and cirrhosis were identified with validated case definitions.[20–23] Coinfection with HBV was defined as a positive HBV surface antigen or HBV DNA in PHO data prior to delivery. A history of alcohol or substance use, obesity and dyslipidemia were defined with ICD coding in CIHI DAD, NACRS and OHIP. For women in the cohort covered under the ODB Plan (~75%), claims for HCV antiviral therapy were described.

Exposures

The primary exposure for perinatal outcome events was positive HCV viremia during pregnancy defined by dichotomizing the pregnancies based on the presence (or lack thereof) of HCV viremia. Pregnancies were HCV viremic if the mother had a positive HCV RNA documented while pregnant or if their last HCV RNA prior to conception was positive with no subsequent negative RNA result. Pregnancies were non-viremic if the mother had evidence of a resolved infection defined by their most recent HCV RNA value prior to childbirth being negative. The primary exposure for the outcome of MTCT was the most recent HCV RNA viral load prior to delivery described in $\log_{10}$ IU/ml.

Outcomes

Perinatal outcome events to 6-weeks post-partum included the maternal outcomes of caesarian section, forceps/vacuum delivery, induction of labor, preterm delivery, antepartum and post-partum hemorrhage, hypertensive complications, gestational diabetes, puerperal infection, intrahepatic cholestasis of pregnancy (ICP), placental abruption, placenta previa. Infant outcomes included birth weight, small/large for gestational age, meconium aspiration, respiratory distress, neonatal jaundice, stillbirth and infant mortality (<1 year) defined using coding outlined in Table S2. The outcome of MTCT was evaluated in the subset of infants born to mothers who remained HCV viremic during pregnancy and if the infant received appropriate HCV screening for HCV antibodies or RNA after birth. We defined appropriate infant HCV screening as receiving either: i) HCV Ab test at 18 months of age[24] or later, or ii) HCV RNA test within 2 to 24 months after delivery, with a maximum follow-up to the end of the study period, December 2018 (based on high predictive value of positive HCV Ab and of earlier HCV RNA testing at 2 months,[25] and because all participants in the cohort had at least 24 months of follow-up). Sensitivity analyses were also performed with alternate definitions for MTCT.

Statistical analysis

Baseline characteristics of the mothers for each pregnancy were compared based on the presence of HCV viremia during pregnancy (As a secondary analysis, baseline characteristics of mothers with HCV were also compared to those without a history of HCV).

The rate of infants who received appropriate HCV screening was calculated using the total number of infants as the denominator. The rate of MTCT was calculated using the total number of infants who received appropriate HCV screening as the denominator.

Two different analyses were conducted to evaluate the association between HCV in pregnancy and perinatal outcomes. First, the association between the presence of HCV viremia during pregnancy (HCV RNA+ *vs.* HCV RNA-) and adverse perinatal outcomes was evaluated with univariate odds ratios (ORs) for each outcome event separately. The independent association between HCV viremia and adverse perinatal outcomes was evaluated in a series of multivariable models adjusting for potential confounders which included age, parity, diabetes, multiple gestation, cirrhosis, alcohol and substance misuse, and HIV coinfection. Secondly, the same analysis was conducted with the primary exposure being changed to 'ever' *vs.* 'never' infected with HCV by using the entire HCV pregnancy cohort (those who were both RNA+ or RNA- during pregnancy) and comparing them to all pregnancies (where the mothers had no history of HCV) in Ontario during the study period, while adjusting for the same confounders outlined above. To evaluate the association between HCV viral load and MTCT, sequential maternal HCV viral load cut-offs were evaluated to determine the association with MTCT using exact logistic regression and adjusting for HIV coinfection and HCV genotype.

Given that 2 exposure-outcome relationships were evaluated, a Bonferroni correction was used and a p value <0.025 was considered statistically significant. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

The creation of the study cohort is shown in Fig. 1. Of 1,988,581 pregnancies over 16 years (in 1,205,966 women), we identified a total of 2,170 pregnancies in 1,636 women who were ever HCV

RNA+ prior to pregnancy with 1,780 (82%) pregnancies which were RNA+ prior/during pregnancy and 390 (18%) who were RNA- during pregnancy (Table 1). Among HCV RNA+ pregnancies, 763 (43%) women had HCV RNA testing during pregnancy, with the majority (79%) having available RNA data during either the second or third trimester (Table 2). Among RNA- pregnancies, 293/390 (75%) were treated through ODB (*i.e.* prescription coverage) and of those, 181 (62%) had a claim for HCV treatment prior to pregnancy. There were 112 (38%) who were covered under ODB but did not have a record of antiviral treatment which were presumed to have spontaneous clearance of HCV and 97 HCV negative pregnancies that were not covered under ODB which had unknown etiology of HCV negativity as this may reflect either spontaneous HCV clearance or antiviral therapy which was obtained through private drug insurance/self-pay (see Table S7 for comparison of pregnancy outcomes between groups based on viremia and history of antiviral therapy). Among RNA+ pregnancies with ODB eligibility, only 51 (4%) had an ODB claim for HCV treatment.

To determine whether HCV RNA levels varied significantly pre-pregnancy and during pregnancy, we identified 229 pregnancies with available HCV RNA measured both pre- and during pregnancy. Of these, 79 (35%) had a >0.5 $\log_{10}$ decrease in viral load, 36 (16%) had a >0.5 $\log_{10}$ increase in viral load, and the

Table 1. Baseline characteristics of MOMBABY births (delivered between January 2000-December 2016) where mother has a positive history of HCV any time prior to conception, stratified by HCV status at time of pregnancy.

Variable	Positive HCV RNA	Negative HCV RNA	Total	*p* value[1]
	n = 1,780	n = 390	N = 2,170	
Demographics				
Maternal age (years)				
Mean ± SD	30.07 ± 5.69	32.01 ± 5.46	30.42 ± 5.70	<0.001
Median (IQR)	30 (26-34)	32 (28-36)	30 (26-34)	<0.001
Advanced maternal age, n (%)				
<35 years	1,367 (76.80)	267 (68.46)	1,634 (75.30)	<0.001
35+ years	413 (23.20)	123 (31.54)	536 (24.70)	
Income quintile, n (%)				
Missing	16 (0.90)	2 (0.51)	18 (0.83)	0.006
1	746 (41.91)	126 (32.31)	872 (40.18)	
2	382 (21.46)	97 (24.87)	479 (22.07)	
3	287 (16.12)	65 (16.67)	352 (16.22)	
4	212 (11.91)	66 (16.92)	278 (12.81)	
5	137 (7.70)	34 (8.72)	171 (7.88)	
Rural residence, n (%)				
Unknown	7 (0.39)	0 (0.00)	7 (0.32)	0.148
Urban	1,577 (88.60)	357 (91.54)	1,934 (89.12)	
Rural	196 (11.01)	33 (8.46)	229 (10.55)	
Parity, n (%)				
Nulliparous	519 (29.16)	117 (30.00)	636 (29.31)	0.741
Parous	1,261 (70.84)	273 (70.00)	1,534 (70.69)	
ODB eligibility, n (%)				
No ODB	465 (26.12)	97 (24.87)	562 (25.90)	0.609
ODB eligible	1,315 (73.88)	293 (75.13)	1,608 (74.10)	
Risk factors				
Elixhauser index				
Mean ± SD	0.41 ± 0.85	0.18 ± 0.53	0.36 ± 0.81	<0.001
Median (IQR)	0 (0-1)	0 (0-0)	0 (0-0)	<0.001
Pre-existing diabetes, n (%)	35 (1.97)	14 (3.59)	49 (2.26)	0.051
Chronic hypertension, n (%)	47 (2.64)	15 (3.85)	62 (2.86)	0.196
HIV coinfection, n (%)	27-36 (1.5-2.0)	<6 (0.2-1.5)	33-37 (1.5-1.7)	0.476
HBV coinfection, n (%)	15 (0.84)	8 (2.05)	23 (1.06)	0.035
Dyslipidemia, n (%)	23 (1.29)	17 (4.36)	40 (1.84)	<0.001
Obesity, n (%)	34 (1.91)	8 (2.05)	42 (1.94)	0.855
Cirrhosis diagnosis, n (%)	160 (8.99)	39 (10.00)	199 (9.17)	0.531
Hepatic decompensation prior to conception, n (%)	5-10 (0.3-0.6)	<6 (<1.5)	8-13 (0.3-0.6)	0.591
History of alcohol use disorder, n (%)	126 (7.08)	8 (2.05)	134 (6.18)	<0.001
History of any substance use disorder, n (%)	413 (23.20)	32 (8.21)	445 (20.51)	<0.001
History of injection drug use disorder, n (%)	456 (25.62)	36 (9.23)	492 (22.67)	<0.001
Gastroenterology visit 1 year prior to or during pregnancy, n (%)	533 (29.94)	98 (25.13)	631 (29.08)	0.058
OB/GYN specialist visit 1 year prior to or during pregnancy, n (%)	1,668 (93.71)	372 (95.38)	2,040 (94.01)	0.206

ODB, Ontario Drug Benefit.
[1]*p* values for categorical variables based on chi-square statistical tests and Fisher's exact test for cell sizes <6. *p* values for mean estimates based on one-way ANOVA tests. *p* values for median estimates based on Kruskal-Wallis tests.

Table 2. Hepatitis C viral characteristics (delivered between January 2000-December 2016) among individuals with HCV RNA+ during or prior to pregnancy (n = 1,780).

HCV characteristics	n (%)
Maternal HCV RNA lab test availability, n (%)	
During pregnancy	498 (27.98)
Prior to pregnancy	1,017 (57.13)
Both	265 (14.89)
If only HCV RNA test prior to pregnancy, months between most recent HCV test and conception date	
Mean ± SD	27.76 ± 25.38
Median (IQR)	21 (9-40)
If only HCV RNA test prior to pregnancy, was most recent test within 1 year prior to pregnancy, n (%)	
N/A	763 (42.87)
No	685 (38.48)
Yes	332 (18.65)
If HCV RNA test during pregnancy, trimester of most recent test prior to delivery, n (%)	
N/A	1,017 (57.13)
1st trimester	164 (9.21)
2nd trimester	286 (16.07)
3rd trimester	313 (17.58)
Maternal HCV genotype, n (%)	
Type 1	972 (54.61)
Type 2	112 (6.29)
Type 3	450 (25.28)
Other (type 4-6)	33 (1.85)
Type mixed/unspecified	213 (11.97)
ODB claim for HCV treatment prior to pregnancy	51 (2.87)
Mom's HCV RNA viral load (IU/ml), n (%)	
Mean ± SD	1,657,839.50 ± 4,203,655.76
Median (IQR)	360,000 (62,200–1,420,000)
N/A	197 (11.07)
≤1 million	1,102 (61.91)
>1 million	481 (27.02)
Mom's HCV RNA viral load (log_{10} IU/ml), n (%)	
N/A	197 (11.07)
<2.5	41 (2.30)
2.5-3.0	38 (2.13)
3.0-3.5	44 (2.47)
3.5-4.0	65 (3.65)
4.0-4.5	108 (6.07)
4.5-5.0	185 (10.39)
5.0-5.5	273 (15.34)
5.5-6.0	345 (19.38)
6.0-6.5	294 (16.52)
6.5-7.0	136 (7.64)
7.0<	54 (3.03)

ODB, Ontario Drug Benefit.

remaining 114 (50%) had a <0.5 log_{10} change in viral load during pregnancy compared to prior to pregnancy.

In pregnancies where the most recent positive RNA was prior to conception, the median time from last positive RNA to conception was 21 months (IQR 9-40). Table 1 shows maternal characteristics among pregnancies with and without HCV viremia. Women were a median age of 30, were predominantly Canadian born/long-term residents (77%), and more often resided in urban settings. Approximately 2% were HIV co-infected. Women with RNA+ pregnancies were younger, more likely to be of lower income quintiles, and have a history of any substance use disorder, including history of injection drug use compared to women with RNA- pregnancies. HCV infections were predominantly HCV genotype 1 (51%, Table 2).

We compared baseline characteristics between ever HCV infected with never HCV infected (Table S4). HCV Ab positive births occurred more often in mothers who were over age 35, lived in lower income quintiles, and were parous. In addition, HCV Ab positive births were more likely to have HIV coinfection, cirrhosis, and history of substance use. After adjusting for confounders, pregnancies in women with a history of HCV had higher odds of perinatal complications including ICP (adjusted OR [aOR] 5.89 95% CI 4.52-7.67, p <0.001), preterm delivery (aOR 1.61, 95% CI 1.41-1.83, p <0.001), post-partum hemorrhage (aOR 1.36, 95% CI 1.14-1.56, p <0.001), and small for gestational age infants (aOR 1.48, 95% CI 1.31-1.67, p <0.001) compared to pregnancies without a history of HCV (Table S5).

Perinatal outcomes in pregnancies by HCV RNA status

Table 3 shows rates of perinatal outcomes in viremic *vs.* non-viremic pregnancies. Women with HCV RNA+ pregnancies were less likely to have cesarean section (31% *vs.* 36%, p = 0.042) and gestational diabetes (6% *vs.* 10%, p = 0.008) but more likely to have preterm delivery (18% *vs.* 12%, p = 0.002), ICP (4% *vs.* <2%, p = 0.003), and post-partum hemorrhage (9% *vs.* 5%, p = 0.013). The median infant birth weight was lower with HCV RNA+ pregnancies (3,119 g *vs.* 3,300 g, p <0.001). In multivariable models, HCV RNA+ pregnancies had increased odds of preterm delivery (OR 1.84, p = 0.0013), post-partum hemorrhage (OR 1.78, p = 0.0173), and ICP (OR 4.55, p = 0.0036) (Table 3) (Table 4).

HCV testing among infants born to mothers with HCV

Among infants born to mothers who were HCV viremic during pregnancy (n = 1,780), 511 (29%, 95% CI 26%-31%) were screened for HCV infection in a manner consistent with guidelines after birth, the majority had HCV Ab testing only at 18 months or later after delivery (n = 345, 68%); others had testing of HCV RNA from 2-24 months only (n = 95, 19%) with the remainder having both HCV Ab and HCV RNA testing (n = 71, 14%). Pregnancy characteristics among those with screening for MTCT compared to those without screening for MTCT are shown in Table S6. Of infants screened with the HCV Ab, 73% were screened at 3 years of age or prior (Table 5). MTCT was observed in 18/511 (4%, 95% CI 1.9-5.2), and there were higher rates of MTCT at higher maternal HCV RNA levels (Fig. 2). Mothers of infants with MTCT were more likely to be nulliparous (p <0.05).

As many infants had HCV testing outside of currently recommended intervals from childbirth to define MTCT, we performed a sensitivity analysis evaluating an earlier cut-off for the definition of MTCT. Using an HCV Ab test sent ≥12 months of age as the criterion, 577/1,995 (29%, 95% CI 27%-31%) of infants born from January 2000 to December 2017 (with 12-month pediatric follow-up) underwent HCV screening. If the criteria included either HCV Ab at least 12 months after delivery or HCV RNA testing within 12 months of delivery, 667 (33%, 95% CI 31%-36%) were screened. Similar results were achieved when using these cut-offs to assess MTCT.

HCV viral load association with MTCT

There were no MTCT events documented in mothers whose HCV RNA value was less than 3.5 log_{10} IU/ml (n = 13), and 13/18 (72%) of MTCT events occurred among those with HCV RNA levels ≥ 6.0 log_{10} IU/ml. When adjusting for maternal HCV genotype (given the univariate association) and HIV coinfection. HCV RNA ≥6 log_{10} IU/ml was significantly associated with MTCT (exact OR 3.38, p = 0.04) (Table 6). There was no significant association of HIV with MTCT when adjusting for HCV RNA (exact OR 3.43, 95%

Table 3. Frequency and proportion of MOMBABY births (n = 2,170) with secondary pregnancy and infant-related outcomes, stratified by HCV status at time of pregnancy.

	Positive HCV infection	No active HCV infection	Total	*p* value[1]
	n = 1,780	n = 390	N = 2,170	
Pregnancy outcomes				
C-section, n (%)	545 (30.62)	140 (35.90)	685 (31.57)	0.042
Forceps or vacuum-assisted delivery, n (%)	130 (7.30)	35 (8.97)	165 (7.60)	0.259
Induction of labor, n (%)	409 (22.98)	98 (25.13)	507 (23.36)	0.363
Preterm delivery, n (%)	318 (17.87)	45 (11.54)	363 (16.73)	0.002
Antepartum uterovaginal hemorrhage, n (%)	203 (11.40)	43 (11.03)	246 (11.34)	0.831
Post-partum hemorrhage, n (%)	165 (9.27)	21 (5.38)	186 (8.57)	0.013
Hypertensive complication[2], n (%)	115 (6.46)	35 (8.97)	150 (6.91)	0.076
Gestational diabetes, n (%)	104 (5.84)	37 (9.49)	141 (6.50)	0.008
Puerperal infection, n (%)	110 (6.18)	24 (6.15)	134 (6.18)	0.985
Intrahepatic cholestasis of pregnancy, n (%)	62–70 (3.5–3.9)	<6 (<1.5)	68–75 (3.1–3.5)	0.003
Placental abruption, n (%)	45 (2.53)	10 (2.56)	55 (2.53)	0.967
Placenta previa, n (%)	21 (1.18)	7 (1.79)	28 (1.29)	0.33
Infant outcomes				
Baby's sex, n (%)				
Female	904 (50.79)	181 (46.41)	1,085 (50.00)	0.117
Male	876 (49.21)	209 (53.59)	1,085 (50.00)	
Multiples at birth, n (%)				
Singleton	1,701 (95.56)	362 (92.82)	2,063 (95.07)	0.024
Multiple birth	79 (4.44)	28 (7.18)	107 (4.93)	
Birth weight (grams)				
Mean ± SD	3,081.62 ± 654.37	3,187.39 ± 631.83	3,100.63 ± 651.50	0.004
Median (IQR)	3,119 (2,719–3,490)	3,300 (2,857–3,600)	3,150 (2,743–3,510)	<0.001
Small for gestational age, n (%)	283 (15.90)	55 (14.10)	338 (15.58)	0.376
Large for gestational age, n (%)	148 (8.31)	27 (6.92)	175 (8.06)	0.361
Meconium aspiration, n (%)	5–10 (0.56)	<6 (0.51)	9–16 (0.55)	1.000
Respiratory distress, n (%)	246 (13.82)	52 (13.33)	298 (13.73)	0.8
Neonatal jaundice, n (%)	252 (14.16)	35 (8.97)	287 (13.23)	0.006
Infant mortality in <1 year, n (%)	12–16 (0.7–0.9)	<6 (<1.5)	14–22 (0.6–1.0)	0.771
Stillbirth, n (%)	<6 (<0.3)	<6 (<1.5)	<6 (<0.3)	0.15

[1]*p* values for categorical variables based on chi-square statistical tests and Fisher's exact test for cell sizes <6. *p* values for mean estimates based on one-way ANOVA tests. *p* values for median estimates based on Kruskal-Wallis tests.
[2]Hypertensive complications include gestational hypertension, eclampsia, pre-eclampsia, and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome.

CI 0.33-18.65, $p = 0.32$), although the total number of HIV-positive patients was small.

Discussion

In a large Canadian population-based cohort of pregnancies in women with a history of HCV infection and linked maternal-infant data, women who remained HCV viremic during pregnancy had increased odds of adverse perinatal outcomes compared to women with cleared HCV infection prior to pregnancy, after adjusting for important confounders. An HCV RNA level of >6 $\log_{10}$ IU/ml was associated with an almost 4-fold higher risk of MTCT. Our findings suggest that not only does clearance of HCV eliminate the risk of perinatal transmission, but it may also reduce the risk of pregnancy complications.

We uniquely demonstrate that active viremia during pregnancy increases the risk of adverse outcomes. This is important as

Table 4. Logistic regression analysis assessing effect of maternal HCV status (main exposure = positive HCV infection, reference group = No active HCV infection) on probability of peripartum outcomes in infants born to mothers with any positive history of HCV.

	Univariate			Multivariate		
Outcomes	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Gestational diabetes[1]	0.58	0.39–0.86	0.0067	0.71	0.47–1.06	0.0958
Intrahepatic cholestasis of pregnancy[2]	3.95	1.43–10.89	0.0079	4.55	1.64–12.64	0.0036
Small for gestational age[3]	1.15	0.84–1.57	0.3760	1.10	0.80–1.51	0.5716
Large for gestational age[4]	1.22	0.80–1.87	0.3615	1.25	0.81–1.93	0.3153
Post-partum hemorrhage[5]	1.80	1.12–2.87	0.0143	1.78	1.11–2.87	0.0173
Antepartum uterovaginal hemorrhage[3]	1.04	0.73–1.472	0.8323	0.99	(0.69–1.42)	0.9706
Preterm delivery[3]	1.67	1.20–2.33	0.0027	1.84	1.27–2.67	0.0013

OR, odds ratio.
[1]Multivariate model adjusted for maternal age, multiple gestation, cirrhosis diagnosis, parity, obesity, history of alcohol use, and history of substance use.
[2]Multivariate model adjusted for maternal age, multiple gestation, and cirrhosis diagnosis.
[3]Multivariate model adjusted for maternal age, multiple gestation, cirrhosis diagnosis, parity, obesity, history of alcohol use, history of substance use, pre-existing diabetes, and HIV coinfection.
[4]Multivariate model adjusted for maternal age, multiple gestation, cirrhosis diagnosis, parity, obesity, history of alcohol use, history of substance use, and pre-existing diabetes.
[5]Multivariate model adjusted for maternal age, multiple gestation, cirrhosis diagnosis, parity, history of alcohol use, history of substance use, pre-existing diabetes, and HIV coinfection.

Table 5. Frequency and proportion of appropriate HCV screening in infants and MTCT in mothers with positive HCV RNA during pregnancy from the MOMBABY cohort (n = 1,780).

	Positive HCV infection, n = 1,780
Appropriate infant HCV screening, n (%)	511 (28.71)
Infant HCV antibody screening 18 months or later after delivery, n (%)	416 (23.37)
Infant age (years) of first HCV antibody screening 18 months or later after delivery, n (%)	
N/A	1,364 (76.63)
18 months to <2 years	178 (10.00)
2 years	83 (4.66)
3 years	41 (2.30)
4 years	33 (1.85)
5 to <8 years	42 (2.36)
8 to <12 years	28 (1.57)
12+ years	11 (0.62)
Infant HCV RNA screening within 2-24 months after delivery, n (%)	166 (9.33)
Infant HCV RNA screening any time after 2 months post-delivery, n (%)	172 (9.66)
HCV MTCT (based on positive result after appropriate infant HCV screening)	
n (%)	18 (1.01)
Rate per infant HCV screening (%)	18/511 (3.52)
HCV MTCT screening result, n (%)	
N/A	1,762 (98.99)
Positive HCV antibody test at 18 months or later after delivery	<6 (<0.3)
Positive HCV RNA test between 2 and 24 months after delivery	<6 (<0.3)
Both positive HCV antibody and RNA tests	8 (0.45)
Positive infant HCV RNA test result any time after 2 months post-delivery, n (%)	15 (0.84)

Appropriate infant screening for HCV defined as infant receiving either: i) an HCV antibody lab test at 18 months or later after birth, or ii) an HCV RNA lab test within 2-24 months after birth.
MTCT, mother-to-child transmission.

previous studies have compared outcomes in HCV Ab-positive pregnancies to pregnancies where the mothers were *never* infected with HCV. As such, previous associations may have been confounded by other factors unique to women of child-bearing age who acquire HCV infection such as co-morbid substance misuse, sociodemographic factors and co-morbid conditions that are also associated with increased adverse pregnancy events. Prior studies

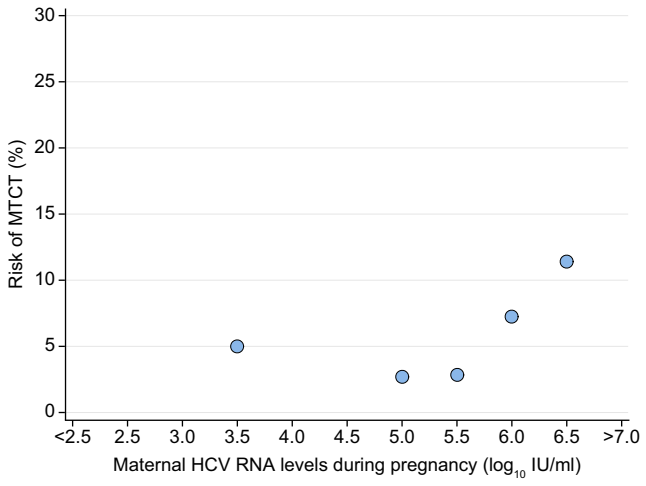

Fig. 2. MTCT risk by HCV viral load. MTCT, mother-to-child transmission.

Table 6. Logistic regression analysis assessing effect of maternal HCV viral load on probability of MTCT in screened infants born to HCV+ mothers (n = 451).

	Univariate			Multivariate		
	eOR	95% CI	*p* value	eOR	95% CI	*p* value
Maternal HCV RNA viral load (log_{10} IU/ml)						
≥6.0	3.94	1.27–13.48	0.0155	3.38	1.07–11.74	0.0373
<6.0	1.00	Ref		1.00	Ref	
HIV coinfection						
Yes	4.61	0.46–23.65	0.1893	3.43	0.33–18.65	0.3174
No	1.00	Ref		1.00	Ref	
Maternal HCV genotype						
Type 1	2.72	0.73–15.11	0.1706	2.33	0.62–13.06	0.2864
Non-type 1	1.00	Ref		1.00	Ref	

eOR, exact odds ratio; MTCT, mother-to-child transmission.

include an observational study of 177 women with positive HCV Ab, who were reported to have an increased risk of ICP and gestational diabetes compared to women with negative HCV Ab.[15] In addition, in a United States population-based retrospective cohort study from 2009-2017 with 94,824 reported cases of maternal HCV infection documented on birth certificate data, associations between maternal HCV with cesarean delivery, preterm birth, small-for-gestational age birth weight, and maternal intensive care unit admission were observed, although the study was limited by unavailability of drug use data or viral load testing.[7] In a study conducted in France of HIV-infected women in the ANRS French Perinatal Cohort, HCV coinfection was associated with ICP and preterm delivery, although its conclusions were limited by the small number of HCV-positive patients (n = 73), and again comparisons were made between HCV-positive pregnancies and HCV Ab-negative pregnancies (as opposed to viremic *vs.* not viremic).[26] Earlier data similarly evaluated outcomes in HCV-positive women compared to women with no history of HCV infection.[16,18,27] Our results support the notion that HCV viremia independently increases the odds of adverse outcomes, and that attaining HCV RNA-status prior to conception could improve perinatal outcomes in this population, although it is important to acknowledge that those individuals with persistent viremia may also be "different" in terms of risk profiles, which may be drivers of pregnancy outcomes.

Our study also demonstrates a potential HCV RNA viral load cut-off which is associated with an increased risk of MTCT, a critical knowledge gap for counselling women with HCV during pregnancy. We suggest that aiming to achieve an HCV RNA <3.5 log_{10} IU/ml (below which we saw no MTCT events) during pregnancy may be a target to reduce the risk of MTCT. A study from Spain of a small cohort of 63 HCV-infected women concluded that higher HCV viremia was associated with increased transmission, but did not identify a viral load cut-off.[28] Similarly, an early study found that higher maternal HCV RNA was seen in infants with MTCT, but did not define thresholds.[29] A prospective study from France which included 78 HCV-positive pregnant women found that infants who had persistent HCV viremia at up to 24 months after birth were more likely to be born to mothers with higher viral loads.[30] On the other hand, other studies have not seen an association between viral load and MTCT.[31–33] These studies have been characterized by different methods for defining MTCT and small cohort sizes. Delineating a viral load cut-off associated with an increased risk

of MTCT will be important for the development of future targeted interventions, such as direct-acting antiviral therapy during pregnancy, which is currently under investigation.[34]

Our study, like other cohorts, demonstrated that screening for HCV among infants born to mothers was inadequate. Less than 30% had HCV screening as recommended by guidelines, and patterns of screening were heterogeneous. There were few infants who had testing after 18 months of age and given data on sensitivity and specificity of earlier HCV RNA testing for MTCT,[25] this may point to the potential benefit of earlier screening for HCV RNA. Although in Ontario all children have universal health coverage (unlike other regions where this may not be the case, and screening rates may even be lower), other factors including patient and provider knowledge on importance of screening and competing priorities, as well as a change in caregiver, may play a role in the very low screening rates.

Our study has unique strengths. We utilized a population-based cohort with linked maternal-infant data and importantly, available follow-up of infants. We also characterized HCV infection accurately by defining it with positive HCV RNA as opposed to HCV Ab alone. Ours was among the largest studies evaluating the issue of HCV viremia and its impact on both MTCT and pregnancy outcomes.

There are limitations to our study. The identification of maternal and infant outcomes was based on diagnostic codes predominantly, so conditions such as ICP may have been underrecognized. Selection bias in developing the cohort could have occurred if we missed RNA+ mothers if their HCV RNA was never checked. Pre-pregnancy HCV RNA may have been different to HCV RNA during pregnancy and could have influenced the HCV RNA threshold of transmission that was identified; however, the effect is likely minimal as most women with pre and during pregnancy HCV RNA values showed minimal variation in absolute RNA level. As not all infants were tested, we only have data available on those with available testing. Our estimates of MTCT are based only on those with available testing and therefore may be an underestimate if MTCT was more common among those without available testing. As cited in prior literature,[35–37] rates of testing of infants to evaluate for MTCT are inadequate and this represents a significant gap in the management of infants born to mothers with HCV. However, we did compare differences in characteristics of the mothers in those infants that underwent recommended screening for MTCT compared to those that did not – only differences noted between groups included younger maternal age, higher nulliparity prevalence, and higher percentage of patients with gastroenterology specialty visit within a year in those who underwent recommended screening for MTCT (Table S6). In addition, the HCV Ab-negative comparison group included people who were never tested for HCV, so it is possible that a small amount of misclassification occurred in individuals who were actually HCV positive but were never tested; that said, given the large numbers and low prevalence of HCV, this is very unlikely to affect the results. There were few patients co-infected with HIV, so HIV data should be interpreted with caution. Data were also collected from a population in Ontario and may not be generalized to other populations internationally. Finally, we are unable to account for other exposures to the infants that may have resulted in horizontal transmission. However, given that all MTCT events occurred under the age of 6 years old, and MTCT is the most likely risk factor for pediatric HCV, we believe that misclassification was unlikely.

In summary, we found that HCV viremia was independently associated with adverse pregnancy outcomes and HCV RNA levels >6 $\log_{10}$ IU/ml were associated with a 4-fold increase in the risk of MTCT with no transmission events observed under 3.5 $\log_{10}$. We also noted that the current patterns of HCV screening in children are inadequate and that over half do not undergo recommended screening. With the recent recommendations for universal HCV screening in pregnancy, and the WHO goal for HCV elimination by the year 2030, as well as emerging data regarding potential antiviral therapy in pregnancy, prioritizing HCV therapy prior to conception among women of child-bearing potential to reduce the risk of MTCT is a high priority. Further defining HCV RNA thresholds associated with risk during pregnancy will be needed to counsel women and optimize outcomes.

Abbreviations

Ab, antibody; CDC, Centers for Disease Control; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICP, intrahepatic cholestasis of pregnancy; MTCT, mother-to-child transmission; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Program; OLIS, Ontario Laboratory Information Systems; OR, odds ratio; PCCF, Postal Code Conversion File; PHO, Public Health Ontario; RNA, ribonucleic acid; WHO, World Health Organization.

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Conflict of interest

TK has served as an Advisor for Gilead and Abbvie. NT has institutional grant support from Gilead, GSK, Helio Health and Roche-Genentech and served as advisor/consultant for Saol Therapeutics, Exigo and Moderna. JAF has consulted for Gilead. MJB reports receiving research support and/or consulting fees from AbbVie, Gilead, McKesson Canada, and Specialty Rx Solutions. JF reports receiving research support and/or consulting fees Abbvie, Gilead, Enanta, Janssen, Roche.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

TK, JAF, and NT developed the concept and design of the study; they verified the underlying data. MD performed all statistical analyses. TK, MD, MB, JAF, NT and JJF interpreted the data. TK, MD, and JAF drafted the initial manuscript. MB, JFF, and NT performed critical revision of the article and draft edits. All authors accept responsibility to submit this manuscript for publication.

Data availability statement

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros

that are unique to ICES and are therefore either inaccessible or may require modification.

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The funding source had no role in the study design, data acquisition/analysis, interpretation of results, or the decision for publication.

Supplementary data

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