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Prospective cohort study of children exposed to hepatitis C virus through a pregnancy screening program

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ABSTRACT

Objectives: Porto Alegre, in south Brazil, has one of the highest hepatitis C virus (HCV) infection rates in the country (84.4 cases/100 000 in 2018). Prenatal screening of HCV, however, has not been routinely offered.

Methods: A longitudinal study of pregnant women with HCV and their infants was conducted between January 2014 and December 2018. Screening for HCV antibodies was offered to all women delivering at the study tertiary institution. HCV RT-PCR was performed if the woman was seropositive. Infants were followed prospectively.

Results: Among 18 953 pregnant women delivering infants during the study period, 17 810 were screened for HCV antibodies (93.9%) with 130 positive results (HCV seroprevalence 0.7%). HCV-RNA was detectable in 57/117 cases (48.7%). HCV viremia was associated with the use of injectable drugs ($P = 0.03$), inhaled/crack drug use ($P = 0.02$), having an HCV-seropositive partner, and $\geq$3 lifetime sexual partners ($P < 0.01$). Genotype 1 was most prevalent (68%) during pregnancy. Among 43 children with follow-up, six (13%) were HCV-infected (transmission rate 13.9%); 50% were infected with genotype 3. Two infants (33%) cleared their infection; the mothers had genetic polymorphisms associated with clearance.

Conclusion: HCV vertical transmission was high in the study population, with HCV infection during pregnancy being vastly underdiagnosed. Public health efforts must focus on this vulnerable population for disease prevention and early treatment.

1. Introduction

In 2015, the World Health Organization (WHO) estimated that chronic hepatitis C affects about 1% of the world population (World Health Organization, 2018). The Brazilian Ministry of Health reported 384 284 cases of hepatitis C virus (HCV) infection between 1999 and 2019 (Brasília DF Ministry of Health, 2020). Positive infections were identified using one of the following markers: HCV antibodies or HCV-RNA. A greater distribution of positive HCV cases was noted in the southeastern (57.7%) and southern (26.7%) regions of Brazil, and rates of HCV in 10 Brazilian capitals exceeded the national average in 2019 (10.8/100 000) (Ministério da Saúde, 2020). Of these cities, Porto Alegre, in the southernmost state of Rio Grande do Sul, stands out as having the highest HCV rate (84.4/100 000) (Ministério da Saúde, 2020).

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According to a review of 26 US Centers for Disease Control and Prevention (CDC)-conducted studies, the estimated HCV seroprevalence in pregnant women in the United States is 1.2% (range 0.1–70.8%) (Schillie et al., 2020). The National Center for Health Statistics showed significant increases in HCV infection among pregnant women and children in the United States from 2011 to 2016 (2.6% to 3.6% and 3.6% to 4%, respectively) (Schillie et al., 2018). Universal screening for HCV in pregnant women was recommended by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America in 2018, as well as by the United States Preventive Services Task Force in 2020, to promote the diagnosis and screening of previously overlooked infections (Ghany et al., 2020; Owens et al., 2020). The CDC also recommends universal screening of pregnant women, except in places where the prevalence of HCV is less than 0.1% (Schillie et al., 2020). In contrast, other entities such as the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the WHO only endorse risk-based screening for HCV (Ministério da Saúde, 2020; Schillie et al., 2020; Hughes et al., 2017). Brazil previously followed a risk-based HCV assessment model, but as of October 2020 has implemented the recommendation of universal HCV triage (Brasília DF Ministry of Health, 2020).

In children, mother-to-child transmission (MTCT) is the main mode of HCV acquisition, but mechanisms associated with transmission are still unclear (Mack et al., 2012; Squires et al., 2017). Fortunately, high rates of spontaneous clearance (25–40%), particularly in the first 24 months following birth, have been observed in the pediatric population (Mack et al., 2012). Maternal HIV co-infection, especially in untreated individuals, is associated with higher rates of HCV vertical transmission (Benova et al., 2014; Checa et al., 2013). Other potential risk factors contributing to MTCT are elevated maternal viral load, amniocentesis, fetal scalp monitoring during labor, and prolonged rupture of the membranes (World Health Organization, 2018; Espinosa et al., 2018; Indolfi et al., 2019).

Inefficient virus transmission to children with perinatal HCV exposure may be explained by immune system defense mechanisms related to human leukocyte antigens (HLA), CD4 lymphocytes, innate immune properties of the placenta, and variations in genes involved in the immune response (Mack et al., 2012; Lapa et al., 2019). In adults, the presence of the C/C genotype in the single nucleotide polymorphism (SNP) rs12979860 and the T/T genotype in the SNP rs8099917 have been associated with both greater spontaneous viral clearance and higher rates of sustained virological response after treatment with pegylated interferon combined with ribavirin (Lapa et al., 2019; Indolfi et al., 2014). Few pediatric studies have investigated the influence of these polymorphisms on HCV viral transmission and spontaneous HCV clearance.

The main objective of this study was to identify the prevalence of HCV in pregnant women in Porto Alegre, Brazil, as well as to compare demographic, behavioral, and biological characteristics of pregnant women with and without detectable HCV-RNA. Additionally, genotypes and polymorphisms present in HCV-viremic mothers and exposed infants were evaluated.

2. Mthods

2.1. Study population and data sources

The Nossa Senhora da Conceição Hospital, located in Porto Alegre, the capital of Rio Grande do Sul, south Brazil, is a public hospital of medium and high complexity care under the Brazilian Unified Health System (SUS), one of the largest public health systems in the world. The institution is a referral hospital for high-risk pregnancies (Boletim Epidemiológico do Hospital Conceição, 2019).

2.2. Study design and selection criteria

A prospective cohort study of pregnant women delivering at Conceição Hospital between January 1, 2014 and December 31, 2018 was conducted. Universal screening for HCV was performed in the hospital maternity ward during the study period. If HCV serology was found to be positive, a quantitative reverse transcription PCR (RT-PCR) for HCV-RNA was performed. Pregnant women with HCV viremia were invited to participate in the study for follow-up of their infants until approximately 36 months after maternal enrollment (Figure 1). Information regarding the HCV test processing, quantification of viral loads, HCV genotyping, the IL28B assay, and HCV case definitions utilized throughout the article are provided in **Supplementary Material** Appendix A (Ghany et al., 2020; Mack et al., 2012; Gélinas et al., 2013; Padua et al., 2016).

2.3. Statistical analysis

To calculate the prevalence of HCV in pregnant women, a binomial analysis was used with the calculation of a simple proportion and 95% confidence interval (CI). Potential differences between maternal demographic, behavioral, and biological characteristics in women with varying levels of detectable HCV-RNA were explored using the Yates or Fisher's Chi-square test. To compare viral load medians, the Mann–Whitney *U*-test was used. Poisson regression was used to determine associations between patient age and detectable HCV viral load. Data were processed and analyzed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). In the comparisons, a correction with the addition of 0.5 was used with the statistical program WinPepi 3.60, when the number zero was found in the contingency tables (Abramson, 2011).

3. Results

Of a total 18 953 pregnant women delivering at Hospital Nossa Senhora da Conceição between January 2014 and December 2018, 17 810 (94%) were screened for HCV by serology. Of these women, 130 had positive results, demonstrating an HCV seroprevalence of 0.7% (95% CI 0.6–0.8%). The HCV-RNA viral load was quantified for 117 (90%) of the 130 HCV-seropositive women, with detectable HCV-RNA identified in 57 women (48.7%). The median time between the date of maternal specimen collection for HCV PCR and date of delivery was 3 days (interquartile range (IQR) −20 to 43.5 days). Fifty-one (87.9%) of 58 eligible infants (87.9%), including a pair of twins, were exposed to active maternal HCV infection (prevalence of 0.3%, 95% CI 0.2–0.4%). Since eight of 51 infants (15.7%) were subsequently lost to follow-up, the presence of HCV infection was evaluated in 43 (74.1%) of 58 HCV exposed newborns (Figure 2). Six infants (14%) were found to be HCV-infected.

Demographic and obstetric characteristics of the pregnant women included in the study are reported in Table 1. The median age of the 117 HCV-seropositive women with detectable HCV-RNA was 30.7 years (range 16–43 years). The majority of the cohort was White (64.1%), most had obtained an elementary school education (55.6%), and most delivered vaginally (55.6%). In addition to HCV, 26 (22.2%) of the 117 women were seropositive for HIV. Half (13 of 26) of those seropositive for HIV had detectable HCV-RNA. Thirteen women with HCV co-infection (11.1%) were co-infected with syphilis (Table 1). No woman in the study tested positive for concurrent hepatitis B virus infection. Compared to those without detectable HCV-RNA levels (only seropositive for hepatitis C), pregnant women with detectable HCV-RNA were significantly older and more likely to have had multiple pregnancies ($P = 0.02$).

Table 2 demonstrates the risk factors associated with maternal HCV exposure in women with either detectable or undetectable HCV-RNA levels. Seventy-one (65.1%) of 109 pregnant women with

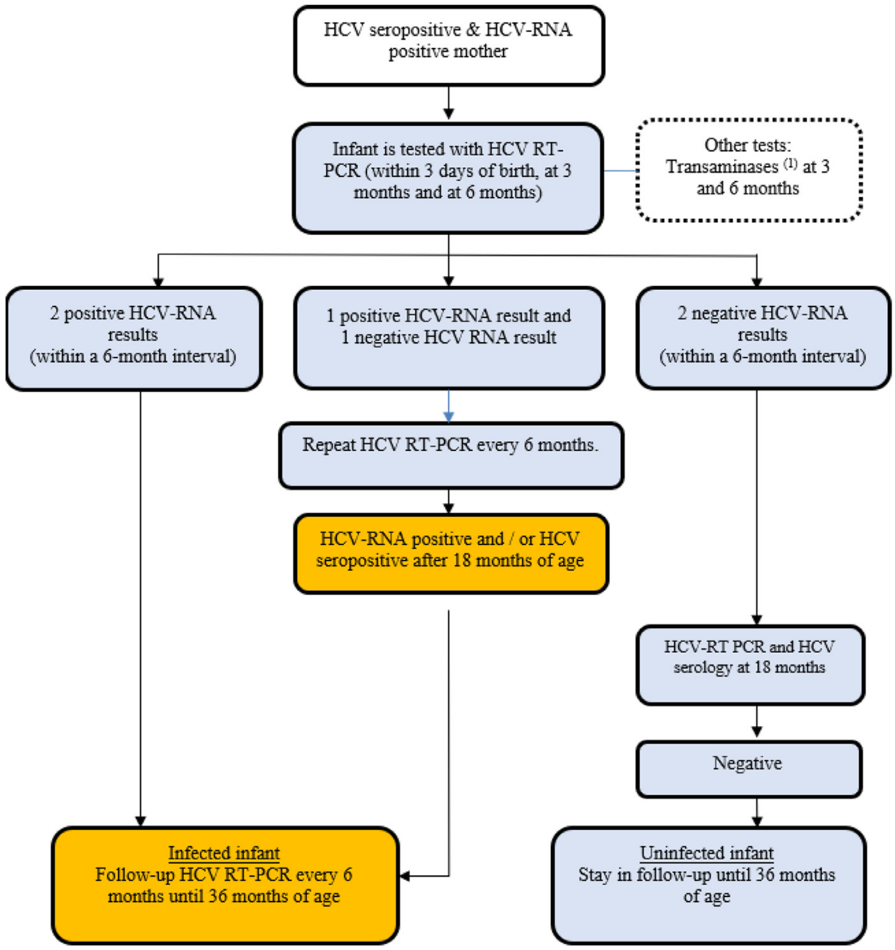

Figure 1. Algorithm for the evaluation of HCV-exposed infants.
Flow diagram of the laboratory assessments performed during the follow-up of infants exposed to HCV.
[a]If an infant had detectable HCV RT-PCR results, transaminases were requested every 6 months up to 3 years of age.

Table 1
Demographic and obstetric characteristics of pregnant women with detectable versus undetectable HCV-RNA

	Total *n* (%)	Pregnant women with detectable HCV-RNA *n* (%)	Pregnant women with undetectable HCV-RNA *n* (%)	RR (95% CI)	*P*-value
Number of women	117 (100)	57 (48.7)	60 (51.3)		
Age (years), median (IQR)	30.0 (16.0–43.0)	32.0 (16.0–43.0)	29.0 (16.0–43.0)	1.04 (1.01–1.07)	0.02*
Race					
White	75 (64.1)	37 (64.9)	38 (63.3)	1.04 (0.70–1.53)	1.00
Education					
Elementary school level	65 (55.6)	33 (57.9)	32 (53.3)	1.10 (0.75–1.60)	0.71
Gravida					
Primigravida	25 (21.4)	7 (12.3)	18 (30.0)	0.52 (0.27–1.00)	0.02*
Type of delivery					
Vaginal	65 (55.6)	37 (64.9)	28 (46.7)	1.48 (0.99–2.22)	0.05
Co-infections					
Syphilis	13 (11.1)	5 (8.8)	8 (13.3)	0.77 (0.38–1.57)	0.56
HIV	26 (22.2)	13 (22.8)	13 (21.7)	1.03 (0.67–1.60)	1.00
	n = 26	n = 13	n = 13		
Detectable HIV viral load (>40 copies/ml)	13 (50.0)	7 (53.8)	6 (46.2)	0.86 (0.40–1.86)	1.00
CD4 >200 cells/µl	24 (92.3)	12 (92.3)	12 (92.3)	1.00 (0.24–4.23)	1.00

CI, confidence interval; HCV, hepatitis C virus; IQR, interquartile range; RR, risk ratio. *$P < 0.05$.

available exposure data reported having at least one of the following risk factors for HCV transmission: injectable drug use, use of crack/inhalable drugs, surgical treatment, dental treatment, tattoo or piercings, blood transfusions, sexual contact, multiple sexual partners, home contact, occupational contact, or accidental contact with biological material. There was no significant difference in the presence of overall risk factors between women with detectable versus undetectable HCV-RNA; 64.2% and 66.1% respectively (P = 0.99). However, a significant association with specific risk factors was identified in the group of pregnant women with

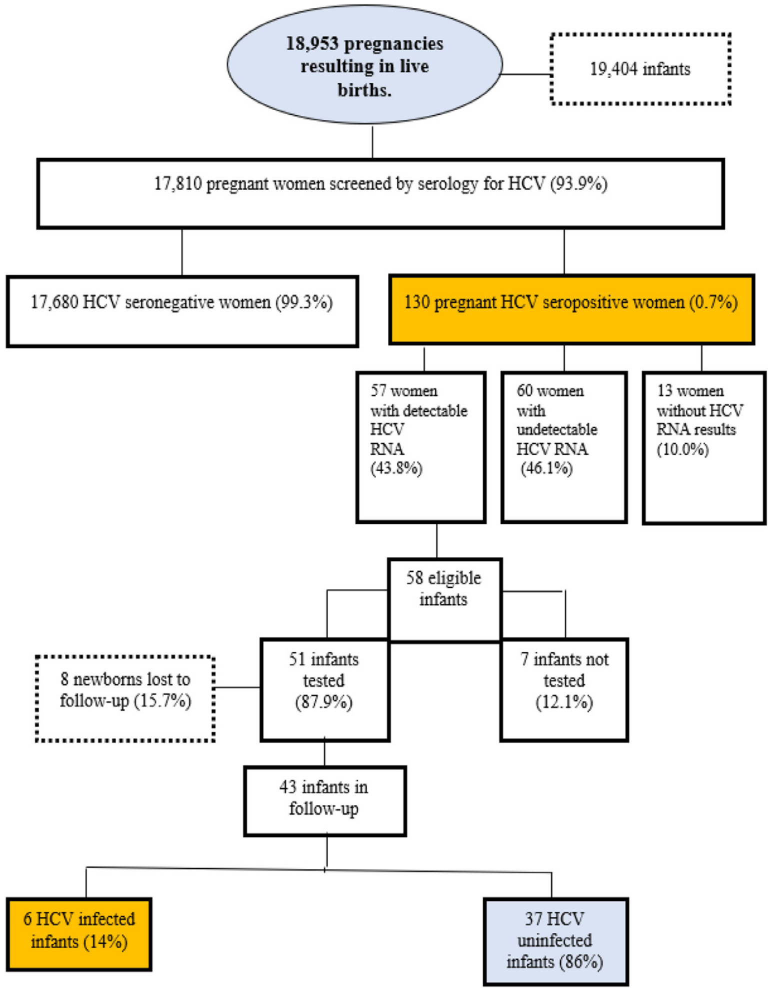

Figure 2. Patient selection flow chart.
HCV screening at delivery between January 2014 and December 2018 (18 953 pregnancies and 19 404 live newborns).
[a]One twin pregnancy was included among the 58 eligible infants born to 57 unique HCV-seropositive mothers.

Table 2
Risk factors for maternal HCV exposure in the HCV-RNA positive and negative groups

n = 117	Total n (%) (n = 109)	Pregnant women with detectable HCV-RNA n (%) (n = 53)	Pregnant women with undetectable HCV-RNA n (%) (n = 56)	RR (95% CI)	P-value
Presence of HCV exposure risk factors	71 (65.1)	34 (64.2)	37 (66.1)	0.96 (0.64–1.43)	0.99
Injectable drugs	28/107 (26.2)	19/53 (35.8)	9/54 (16.7)	1.58 (1.10–2.26)	0.03*
Acupuncture[a]	2/107 (1.9)	0/53 (0.0)	2/54 (3.7)	0.21 (0.01–4.30)	0.50
Inhalable/crack drugs	14/107 (13.1)	11/53 (20.8)	3/54 (5.6)	1.74 (1.22–2.48)	0.02*
IDU[a]	3/107 (2.8)	3/53 (5.7)	0/54 (0.0)	6.75 (0.36–127.6)	0.12
Surgical treatment	45/106 (42.5)	18/52 (34.6)	27/54 (50.0)	0.72 (0.47–1.09)	0.16
Dental treatment	50/107 (46.7)	21/53 (39.6)	29/54 (53.7)	0.75 (0.50–1.11)	0.21
Tattoo or piercing	51/108 (47.2)	20/54 (37.0)	31/54 (57.4)	0.66 (0.44–0.98)	0.05
Blood transfusion	16/108 (14.8)	8/53 (15.1)	8/55 (14.5)	1.02 (0.60–1.74)	1.00
Sexual contact	13/91 (14.3)	11/43 (25.6)	2/48 (4.2)	2.06 (1.45–2.93)	0.01*
≥3 sexual partners	35/106 (33.0)	25/53 (47.2)	10/53 (18.9)	1.81 (1.27–2.59)	0.01*
Household contact	12/93 (12.9)	8/45 (17.8)	4/48 (8.3)	1.46 (0.92–2.32)	0.22
Occupational contact	4/92 (4.3)	3/45 (6.7)	1/47 (2.1)	1.57 (0.86–2.88)	0.36
Accident with biological material	2/104 (1.9)	1/50 (2.0)	1/54 (1.9)	1.04 (0.26–4.22)	1.00

CI, confidence interval; HCV, hepatitis C virus; IDU, injecting drug user; RR, risk ratio. *P < 0.05.
[a] The Agresti correction was used to compare the groups (WinPepi version 11.5).

detectable HCV-RNA, including injectable drug use (P = 0.03), inhalable/crack drug use (P = 0.02), sexual contact with an HCV-seropositive partner (P = 0.01), and reports of three or more sexual partners. In contrast, 57.4% of women with undetectable HCV-RNA reported having tattoos or piercings compared to only 37% of women with detectable HCV-RNA. Only a few patients with detectable and undetectable HCV-RNA (approximately 15% in each group) reported a previous blood transfusion (Table 2). No pregnant woman in this study had a history of hemodialysis or organ transplantation that would increase their risk of exposure to HCV.

A total of 58 infants (one pair of twins) were born to HCV-seropositive mothers with detectable HCV-RNA and 60 infants

Table 3
HCV mother-to-child transmission cases according to maternal and neonatal factors

$n = 6$	Case A	Case B	Case C[a]	Case D	Case E	Case F
Maternal factors						
Date of delivery	08/01/2014	01/09/2016	12/14/2016	12/11/2015	01/09/2018	11/21/2018
Type of delivery	Vaginal	Vaginal	Cesarean	Cesarean	Vaginal	Cesarean
HCV viral load at delivery	2 108 206	28 744	2 053 219	31 422	4 836 313	690 433
Genotype	3	3	1a	1a	1a	3
Interleukin 28B RS 129/RS 809	CC/TT	CC/TT	TT/GG	Not done	Not done	Not done
Use of inhaled drugs or crack	Yes	No	Yes	No	No	No
Injection drug use	No	No	No	Yes	No	No
HBsAg	Non-reactive	Non-reactive	Non-reactive	Non-reactive	Non-reactive	Non-reactive
Anti-HIV	Non-reactive	Non-reactive	Reactive	Reactive	Non-reactive	Non-reactive
HIV viral load (cop/ml)	Not infected	Not infected	Not infected	1383	Not infected	Not infected
RPR	Non-reactive	Non-reactive	Non-reactive	Non-reactive	Non-reactive	Non-reactive
Neonatal factors						
Classification	Transient viremia	Transient viremia	Infected	Infected	Infected	Infected
Sex	F	M	M	F	M	F
Gestational age (months)	39	41	37.6	39	39	38
Birthweight (grams)	2905	3860	4290	2970	3500	3645
First detectable HCV viral load units	3 638 534	20 140	53 871	31 422	107	87 974
Age at collection of the first detectable HCV VL (months)	7	12	5	34	0	84
Age of spontaneous clearance (months)	35	18	NA	NA	NA	NA
Genotype	NA	NA	1b	1a	1a	3
Interleukin 28B rs12979860/rs8099917	CC/TT	CT/TT	CT/GT	Not done	Not done	Not done
HCV serology (age in months)	Non-reactive(13.0)	Non-reactive(18.6)	Reactive(26.6)	Reactive(38.4)	Reactive(26.0)	Reactive(23.0)
Maximum ALT (age, months)[b]	21 (12)	31 (14)	344 (4)	88 (4)	53 (25)	32 (3)

ALT, alanine aminotransferase; F, female; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; M, male; NA, not applicable; RPR, rapid plasma reagin test; VL, viral load.
[a] Mother with active *Mycobacterium tuberculosis* infection; the child received prophylactic isoniazid up to 3 months of life.
[b] Reference values for the ALT upper limit: boys <60 U/l, girls <55 U/l.

were born to HCV-seropositive mothers without detectable HCV-RNA ($n = 118$ infants, $n = 117$ mothers) (**Supplementary Material** Table S1, Appendix B). HCV-RNA PCR was performed in early specimens of 51 (87.9%) of 58 exposed infants, of whom 43 (84.3%) remained in follow-up. Six of the 43 infants were infected with HCV, resulting in an HCV MTCT rate of 13.9% (95% CI 5.3–27.9%). Spontaneous viral clearance occurred in two (33.3%) of the six children infected with HCV. A description of these cases is given in Table 3. **Supplementary Material** Table S1 in Appendix B compares the 58 infants of the 57 viremic mothers to the 60 infants of the 60 non-viremic mothers. No significant differences were identified between infants born to mothers with detectable versus undetectable HCV-RNA regarding birthweight, gestational age, or HIV infection (**Supplementary Material** Table S1). The overall frequency of low birthweight and prematurity in the infants was 16.1% and 14.4%, respectively. Although 26 (22%) of 118 newborns were exposed to HIV, only one (4%) of 26 tested positive for HIV. In this case, the infected infant's mother had detectable HIV-RNA close to delivery.

Supplementary Material Table S2 in Appendix B examines viral markers and host genetic factors of pregnant women and their infants according to HCV MTCT. The median HCV viral load among 57 pregnant women with detectable HCV-RNA was 560 554 IU/ml (range 8040–8 375 380 IU/ml; IQR 186 381–2 045 941 IU/ml). Genotype 1 was most frequently identified in women with detectable HCV-RNA levels (39 of 57 women, 68.4%), with 20 cases of subtype 1a, 11 cases of subtype 1b, and eight cases without a defined subtype. Genotypes 3 and 2 were less common and were present in 14 (24.6%) and one (1.7%) of 57 cases, respectively. Genotype results were unavailable in three (5.3%) of 57 cases. Maternal factors associated with HCV MTCT were also examined in the 43 infants born to mothers with detectable HCV-RNA. While 16 of 43 newborns (37.2%) were delivered via cesarean section, half (3 of 6) of the HCV-infected newborns were delivered via cesarean section. HCV-positive infants were also more frequently infected with genotype 3, born to mothers with uncontrolled HCV viral loads of greater than 600 000 IU/ml, and born to mothers with an HIV co-infection. However, findings were not statistically significant (**Supplementary Material** Table S2, Appendix B). The two infants who achieved HCV viral clearance were born to mothers who had a C/C genotype rs12979860 IL28B and TT genotype rs8099917 (Table 3). Given the small number of infant HCV infections, it was not possible to explore potential associations between maternal/infant IL28B polymorphisms and spontaneous viral clearance.

4. Discussion

The seroprevalence of HCV in the pregnant women in this study was 0.7%. This falls at the higher end of HCV prevalence in pregnant women reported throughout Brazil, ranging from 0.1% to 1.3% (Gardenal et al., 2011; Fernandes et al., 2014; Gomes et al., 2016; Batistão et al., 2017; Barros et al., 2018). A subset (0.3%) of pregnant women in the study cohort were found not only to be HCV-seropositive, but also to have detectable HCV-RNA levels around the time of delivery. Rates of detectable HCV viremia in pregnant women in this study are within the range of 0.09% to 2.4% reported in the literature (El-Kamary et al., 2015; Jhaveri et al., 2015; Kopilović et al., 2015; Orkin et al., 2016). HCV prevalence in pregnant women living in southern Brazil is likely even greater than that reported in the present study. Only recently did the Brazilian Ministry of Health draft guidelines recommending universal screening for HCV in pregnant women during the first prenatal consultation (Brasília DF Ministry of Health, 2020). Self-reported HCV risk assessment is an unreliable measure of true disease prevalence and leaves room for missed diagnostic opportunities.

At an underestimated 13.9%, the rate of HCV MTCT found in the present study is notably elevated when compared to transmission rates ranging from 6% to 14% identified in larger prospective studies (Jhaveri et al., 2015; Ceci et al., 2001; Resti et al., 2002).

Probable risk factors associated with HCV MTCT include elevated maternal viral load, HIV co-infection, and female sex of the infant (Mack et al., 2012; Benova et al., 2014; Mariné-Barjoan et al., 2007; Ngo-Giang-Huong et al., 2010; Pembrey et al., 2005). No risk factors were associated with HCV transmission in this cohort, likely due to the small number of transmission events noted. Similarly, it was not possible to assess the relationship between the presence of IL28B polymorphisms and MTCT as a result of the limited sample size and lack of serial HCV-RNA specimens in exposed infants. However, the two infants who eradicated their infection possessed genetic polymorphisms associated with spontaneous clearance.

Previous studies have focused on the relationship between HCV and self-identified Black race. In a cohort study that evaluated the epidemiology of chronic liver diseases, it was observed that chronic HCV infection with or without cirrhosis was more frequent in African Americans compared to other ethnicities (Setiawan et al., 2016). In contrast to other areas in Brazil, the majority of pregnant women in the present study self-identified as White. The predominance of the White race is unique to southern Brazil and reflects European immigration to this region, where approximately 90% of the population is of European ancestry (Ruiz-Linares et al., 2014). We also found that the majority of women in this study had not completed education beyond elementary school. Lower educational level is consistent with the demographics of patients utilizing free public health systems in Brazil.

Characteristics of pregnant women with detectable HCV-RNA were older age, multiparity, and history of vaginal delivery. Although previous research has shown an association between HCV seropositivity and concurrent HIV and syphilis co-infections, no relationship between HIV or syphilis co-infections and the presence of detectable HCV-RNA was found (Yeganeh et al., 2015; Adachi et al., 2018). Further, detectable HCV-RNA did not appear to have any effect on HIV disease severity in pregnant women with HIV co-infections. HIV viral loads and absolute CD4 values did not differ significantly between pregnant women with HIV co-infections with and without detectable HCV-RNA. The role of co-infections in HCV MTCT was also examined. No transmission events occurred in infants born to VDRL-positive mothers, and two of six transmission events occurred in infants born to HIV co-infected mothers. One of these mothers had detectable HIV-RNA and was being treated irregularly, while the other had undetectable HIV-RNA and was receiving complete treatment (Table 3). The number of transmission events in this study was too small to draw any definite conclusion regarding the association between maternal co-infections and HCV MTCT.

An association was found between detectable HCV-RNA and prior use of inhalable/crack drugs, sexual contact with an HCV-infected partner, and multiple sexual partners. Intranasal transmission of HCV infection was supported through a study that found the presence of blood and viral HCV-RNA in nasal secretions and drug-sniffing equipment among non-injection drug users in New York City (Aaron et al., 2008). In the present study, the exposure factor most strongly associated with detectable HCV-RNA was sexual contact with an HCV-infected partner. Monogamous relationships are not protective against obtaining a sexually transmitted infection (Terrault et al., 2013). In fact, there are several reasons why people in relationships may be reluctant to disclose infections, including infidelity, cultural stigma, and fear of domestic abuse (Andrade et al., 2015). Conversely, the presence of tattoos was more frequent in HCV-seropositive patients who did not have detectable HCV-RNA.

Newborns with HCV exposure have a higher risk of prematurity, low birth weight, and congenital anomalies (Huang et al., 2016; Stokkeland et al., 2017). In a meta-analysis of seven observational studies, a higher occurrence of intrauterine growth restriction and low birth weight was observed in newborns of mothers with chronic HCV (Huang et al., 2016). Infant birth outcomes were evaluated according to the presence of maternal HCV-RNA levels and no significant differences in neonatal characteristics (including birth weight and gestational age) were found when stratifying by the presence of maternal HCV-RNA viremia. This may be due to the fact that HCV-RNA levels were not monitored serially throughout pregnancy. HCV infection may impact pregnancy and neonatal outcomes regardless of viremic peaks. In the HCV-seropositive cohort in the present study, prematurity was present in 14% of cases and low birth weight was seen in 16% of infants, which is slightly higher than the rates noted for the general Brazilian population in 2018 (11% prematurity and 6% low birth weight) (Silveira et al., 2018).

With universal prenatal HCV screening, six infants with HCV were identified, who received early linkage to care and monitoring that might otherwise have been missed. Challenges with patient follow-up in this study required additional effort from the research team to encourage testing of exposed infants. Several children were actively searched for to ensure visit attendance, even involving social services in some cases. Regardless, it was possible to follow-up 84.3% of the cohort. The obstacle of patient follow-up is experienced in locations outside of Brazil as well. The Philadelphia Department of Public Health concluded that the vast majority of children exposed to HCV do not undergo routine follow-up (Kuncio et al., 2016). These findings were reinforced in a Tennessee Medicaid study that found HCV testing only occurred in one of four children perinatally exposed to HCV (Lopata et al., 2020).

Limitations of this study include the small number of HCV transmission events, the relatively modest sample size of HCV-seropositive women, and the difficulties in keeping this population of infants in follow-up for 36 months. Nevertheless, the study results reinforce the recent recommendation made by the Ministry of Health of Brazil regarding universal screening for HCV in pregnant women (Brasília DF Ministry of Health, 2020).

Public health initiatives that focus on HCV screening and follow-up during prenatal care visits are important strategies to prevent MTCT. Universal HCV screening is cost-effective and has the potential to reduce long-term morbidity through linkage to referral and treatment services (Espinosa et al., 2018; Selvapatt et al., 2015; Tasillo et al., 2019; Kushner et al., 2019). During the prenatal period, women are in direct contact with the healthcare system, presenting a crucial opportunity for HCV infection screening and referral for follow-up visits and exposed newborn testing. The study findings emphasize the identification of patients at risk, and early infant diagnosis must be prioritized, particularly as new treatment modalities for HCV become available to this population.

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Author contributions

RBP, ARLR, LJTP, IRSV, KC, and KNS established the study concept and design. IRSV, RBP, and EJS conducted the statistical analysis. RBP, ARLR, LJTP, EJS, MCC, IRSV, and KNS interpreted the data analysis and study results. All authors contributed to the overall study conduct, manuscript writing and editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.07.019.

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