Hepatitis C Infection Among Pregnant Women in British Columbia: Reported Prevalence and Critical Appraisal of Current Prenatal Screening Methods

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ABSTRACT

Background: Despite the fact that hepatitis C virus (HCV) is a relatively common infection in Canada, particularly in British Columbia (BC), there is a paucity of information on actual HCV prevalence in pregnant women. At present, pregnant women are only screened if they fit risk criteria, which may result in under-identification of HCV in this population. The purpose of this study was to determine the overall prevalence rate, age and geographic distribution of reported HCV infection among pregnant women in BC, and compare results to a previously conducted anonymous seroprevalence survey.

Methods: Reported HCV prevalence was determined through a confidential database linkage of all prenatal screening results at the Canadian Blood Services (CBS) with all HCV test results at the Provincial Laboratory, from May 2000 to Oct 2002. Data were stratified by age group and geographic location, and subsequently compared to an anonymous prenatal seroprevalence survey conducted in 1994.

Results: The overall HCV prevalence rate was 50.3/10,000 (95% CI 46.3-54.6), or 0.5% of the cohort. Prevalence was highest in the northern BC region (66.2/10,000, 95% CI 51.4-85.3) and lowest in the populous suburban region southwest of Vancouver (38.0/10,000, 95% CI 32.3-44.8). Of note, the rate of reported HCV among pregnant women was significantly lower than the anonymous seroprevalence rate: 50.3/10,000 vs. 91.3/10,000 ($p < 0.0001$).

Conclusion: Rates of reported HCV among pregnant women were approximately 50% lower than the rates determined by the anonymous seroprevalence survey. Further research is needed to determine the relative merits of the current selective screening policy versus universal prenatal HCV screening in pregnancy.

Key words: Hepatitis C virus; pregnancy; mother to child transmission; prenatal testing

La traduction du résumé se trouve à la fin de l'article.

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Hepatitis C virus (HCV) is a serious blood-borne infection affecting approximately 180 million people worldwide.¹ More than 250,000 individuals are currently living with HCV in Canada, with 5,000 new infections projected annually.² In British Columbia (BC), the reported HCV prevalence is almost twice the national rate: 66.2/100,000 versus 35.8/100,000.³ It is estimated that one of every 120 women who gives birth in Canada is infected with HCV.⁴ There were 377,000 births in Canada in 2008/2009,⁵ thus approximately 3,142 births were to HCV-infected women. With a vertical transmission risk of 4-6%,⁶⁻⁸ it is possible that between 126-189 Canadian-born children may have been infected with HCV at birth.

To reduce the risk of vertical transmission among pregnant women at risk of HCV infection, the Society of Obstetricians and Gynaecologists of Canada (SOGC) currently recommends risk factor-based prenatal screening (Figure 1).⁴ However, as the validity of this method is dependent on active assessment of risk factors by health care providers and full disclosure from patients, up to 60% of HCV-infected pregnant women may be "missed".⁴ More comprehensive screening programs for HCV in pregnancy would permit detection of infection in asymptomatic young women, enable women to receive antenatal and postpartum HCV care, and provide an opportunity to screen and treat infants at risk for infection. As there is limited information on baseline infection rates among pregnant women in Canada, neither the true burden of HCV nor

the potential benefits of enhanced screening of the pregnant population have been properly assessed.

Our objectives were to 1) determine the prevalence rate of reported HCV using a population-based survey of pregnant women in BC, and 2) using age and regional distribution data, compare the rates of reported HCV infection to a seroprevalence survey of pregnant women conducted previously.

METHODS

Study design, participants, inclusion criteria and setting

The preliminary data presented here were collected during the recruitment phase of a prospective study investigating vertical transmission of HCV. HCV-positive pregnant women were identi-

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Figure 1. Women in these risk categories should be offered screening for hepatitis C

- Injection drug user (ever)
- Haemodialysis
- Persistently elevated ALT*
- Recipients of clotting factor concentrates before 1988
- Recipients of blood components or solid organs before 1992
- Recipients of blood components or solid organs from HCV (+) individual
- Significant exposure to blood of HCV (+) individual or that of individual at high risk
- Prisoners in correctional facilities
- HIV-positive individuals
- Individuals with tattoos (especially performed in prisons)

Source: SOGC (2000)⁴

* ALT=alanine transaminase

fied through a confidential database linkage between the Canadian Blood Services (CBS), which contains nominal data on all pregnant women who undergo routine prenatal blood testing, and the Public Health Information System (PHIS) at the BC Centre for Disease Control (BCCDC), which contains nominal data for all laboratory-confirmed HCV-antibody positive individuals in the province. Data were cross-matched using name, date of birth (DOB), and personal health number (PHN). Data linkage occurred, and remained, within the BCCDC. The resulting cohort of HCV-positive pregnant women were later contacted through their primary health care provider regarding participation in a prospective study. This study received approval from the University of British Columbia Clinical Research Ethics Board (C00-0176), and institutional authorization from the CBS and the BCCDC.

During the study period, 137,369 women had CBS routine prenatal blood work completed. Duplicate, mismatched and incomplete records were removed. The derivation of the final dataset of 109,983 is outlined in Figure 2. For analyses, data were stratified into three age categories: 15-24, 25-34 and 35-44 years; due to low numbers, women younger than 15 or older than 44 years were removed. The data were stratified into provincial Health Authorities using care provider postal codes. The health governance structure of BC consists of five Health Authorities (HA): 1) Northern Health, which consists of 300,000 people spread across nearly two thirds of the province, including many remote and rural communities, and the highest proportion of Aboriginal persons (13%); 2) Interior Health, which consists of 723,000 people and the largest proportion of people over 65 years of age, residing in a few larger municipalities (e.g., Kelowna, Kamloops) as well as remote and rural regions; 3) Vancouver Island Health, which serves over 750,000 people living on Vancouver Island; 4) Vancouver Coastal Health, which consists of over 1 million people residing in Vancouver, Richmond and North and West Vancouver; and 5) Fraser Health, serving the 1.5 million people who live in suburban areas surrounding Vancouver.

Data measurement

As per standard protocol in BC at the time, hepatitis C seropositivity was determined by two sequential enzyme immuno-assays (EIA) to detect anti-HCV antibodies. The primary screen was Abbott AxSYM HCV v. 3.0 (Abbott Diagnostics, Mississauga, ON) and the supplementary screen was Ortho Vitros Eci Anti-HCV (Ortho-Clinical Diagnostics, Markham, ON). If the initial EIA was positive, a second confirmatory EIA was performed. Discordant EIA results were reported as indeterminate. Reactive sera at the lower limit of detection were reported as weakly reactive. Hepatitis C tests that

Figure 2. Flow of participants to derive the Study Dataset

were indeterminate or weakly reactive were considered seronegative.

Prevalence rates of reported HCV infection were compared with an unpublished anonymous seroprevalence survey conducted in 1994 among pregnant women in BC (D. Pi, unpublished data). All standard prenatal samples (N=14,780) received by the Canadian Red Cross, Vancouver Centre, between January and April 1994 were tested for anti-HCV antibodies (Ortho HCV EIA v. 2.0, Ortho-Clinical Diagnostics Inc. Raritan, NJ); EIA-reactive specimens were confirmed by recombinant immunoblot assay (Ortho HCV RIBA-2, Ortho-Clinical Diagnostics Inc. Raritan, NJ). Indeterminate HCV RIBA confirmatory test results were considered seronegative. Anti-HCV antibody EIA tests were performed at the Canadian Red Cross, Vancouver Centre, and HCV RIBA tests at the Canadian Red Cross, National Office, Ottawa. Data were stratified by age group (15-24, 25-34 and 35-44 years) and residence location (Lower Mainland and Other).

Statistical methods

Statistical analyses were performed with SAS version 8.0 (SAS Institute Inc., Cary, NC, USA). Reported rates of HCV per 10,000 persons

Table 1. Hepatitis C Test Status and Test Results Stratified by Age Group and Geographic Location of 109,983 Pregnant Women in the HCV Dataset

Health Authority	Age Group	Total	HCV test (%)	Test statistic/ p-value	HCV positive (%)	Prev/10,000	95% CI	Test statistic/ p-value
Fraser	15-24	8029	1707 (21.3)	$\chi^2=55.0$	32 (1.9)	39.9	28.3-56.2	$\chi^2=4.9$
	25-34	23,008	3989 (17.3)	<0.0001	77 (1.9)	33.5	26.8-41.8	NS
	35-44	6043	1173 (19.4)		32 (2.7)	53.0	37.6-74.7	
	Total	37,080	6869 (18.5)		141 (2.1)	38.0	32.3-44.8	
Interior	15-24	4008	611 (15.2)	$\chi^2=17.1$	15 (2.5)	37.4	22.8-61.6	$\chi^2=7.7$
	25-34	7841	996 (12.7)	<0.0002	36 (3.6)	45.9	33.2-63.5	<0.025
	35-44	2023	323 (16.0)		18 (5.8)	89.0	56.6-140.2	
	Total	13,872	1930 (13.9)		69 (3.6)	49.7	39.4-62.9	
Northern	15-24	3178	601 (18.9)	$\chi^2=18.1$	26 (4.3)	81.8	56.0-119.6	$\chi^2=1.8$
	25-34	4788	704 (14.7)	<0.0001	28 (4.0)	58.5	40.6-84.4	NS
	35-44	947	146 (15.4)		5 (3.4)	52.8	23.3-112.7	
	Total	8913	1451 (16.3)		59 (4.1)	66.2	51.4-85.3	
Vancouver Coastal	15-24	3590	847 (23.6)	$\chi^2=38.2$	24 (2.8)	66.9	45.1-99.3	$\chi^2=1.5$
	25-34	20,886	4306 (20.6)		107 (2.5)	51.2	42.4-61.9	
	35-44	9726	2682 (27.6)		50 (1.9)	51.4	39.1-67.7	
	Total	34,202	7836 (22.9)		181 (2.3)	52.9	45.8-61.2	
Vancouver Island	15-24	4141	1303 (31.5)	<0.0001	26 (2.0)	62.8	43.0-91.8	$\chi^2=6.0$
	25-34	9034	2228 (24.7)		50 (2.2)	55.3	42.1-72.9	
	35-44	2741	753 (27.5)		27 (3.6)	98.5	68.0-142.9	
	Total	15,916	4284 (26.9)		103 (2.4)	64.7	53.4-78.4	
Total province	15-24	22,946	5069 (22.1)	$\chi^2=199.2$	123 (2.4)	53.6	45.0-63.9	$\chi^2=8.8$
	25-34	65,557	12,223 (18.6)	<0.0001	298 (2.4)	45.5	40.6-50.9	<0.015
	35-44	21,480	5077 (23.6)		132 (2.6)	61.5	51.9-72.8	
	Total	109,983	22,369 (20.3)		553 (2.5)	50.3	46.3-54.6	

Table 2. Comparison of HCV Seroprevalence Between Anonymous Testing (1994) and Database Cross-Matching (2000-2002) With Indeterminate and Weakly Reactive Tests Excluded

Location	Age group	Anonymous Seroprevalence Survey (n=14,780; 1994)			HCV Dataset (n=22,369; 2000-02)			p-value
		No.	Total	Prevalence/10,000 (95% CI)	No.	Total	Prevalence/10,000 (95% CI)	
Lower Mainland	15-24	14	1668	83.9 (47.8-144.1)	56	11,619	48.2 (37.2-62.5)	NS
	25-34	41	4772	85.9 (62.5-117.5)	184	43,894	41.9 (36.3-48.4)	<0.001
	35-44	21	1065	197.2 (125.6-305.2)	82	15,769	52.0 (41.9-64.5)	<0.001
	Total	76	7505	101.3 (80.4-127.3)	322	71,282	45.2 (40.5-50.4)	<0.001
Other	15-24	17	2487	68.4 (41.2-111.7)	67	11,327	59.2 (46.6-75.1)	NS
	25-34	34	4064	83.7 (25.2-68.4)	114	21,663	52.6 (43.9-63.2)	<0.05
	35-44	8	724	110.5 (57.6-218.7)	50	5711	87.6 (66.6-115.2)	NS
	Total	59	7275	81.1 (62.3-105.2)	231	38,701	59.7 (52.5-67.9)	<0.05
All	15-24	31	4155	74.6 (51.6-107.1)	123	22,946	53.6 (45.0-63.9)	NS
	25-34	75	8836	84.9 (67.3-106.9)	298	65,557	45.5 (40.6-50.9)	<0.001
	35-44	29	1789	162.1 (110.8-235.1)	132	21,480	61.5 (51.9-72.8)	<0.001
	Total	135	14,780	91.3 (76.9-108.4)	553	109,983	50.3 (46.3-54.6)	<0.001

Lower Mainland = Vancouver Coastal and Fraser Health Authorities

and 95% confidence intervals were calculated for each age stratum and for all ages combined, and within each HA and for the entire province. Health Authority data were aggregated into Lower Mainland (Vancouver Coastal and Fraser) and Other (remaining HAs) for comparison to the anonymous seroprevalence survey. Bivariate categorical data were analyzed using Pearson's chi-square; p-values less than 0.05 were considered statistically significant.

RESULTS

Of the 109,983 women, 20% (22,369) had been tested for HCV. There was significant variation in the proportion of women tested across provincial regions (Table 1). HCV testing rates were highest in the Vancouver Island HA (27%), and lowest in the Interior HA (14%), versus all other BC regions (Table 1; $p<0.01$ for all pairwise comparisons). There was significant variation in HCV testing rates across age categories: highest rates of testing occurred among women aged 35-44 (24%), followed by women aged 15-24 (22%), with lowest rates of testing among women aged 25-34 (19%; Table 1; $p<0.002$ for all pairwise comparisons). Of the 22,369 women tested, 553 were HCV positive, of whom 22% were 15-24, 54% were

25-34, and 24% were 35-44 years of age (Table 1). Approximately 58% of HCV-positive women were from the Lower Mainland, and the remaining 42% were from other BC regions. Overall, the provincial prevalence rate of reported HCV was 50.3/10,000 (95% CI 46.3-54.6) or 0.5% (553/109,983) of the study population.

There was significant variation in reported HCV prevalence across provincial regions (Table 1). Reported prevalence was highest in the Northern HA (0.7%) and lowest in the Fraser HA (0.4%) (Table 1; $\chi^2 = 13.17$, df 1, $p=0.0003$). The HCV prevalence rate in the Fraser HA was also significantly lower than that reported for the Vancouver Coastal ($\chi^2 = 8.78$, df 1, $p=0.003$) and Vancouver Island ($\chi^2 = 17.31$, df 1, $p<0.0001$) HAs. There was significant variation in reported HCV prevalence across age categories: HCV prevalence was highest among 35-44 year old women (0.006%); however, this only differed significantly from 25-34 year old women ($\chi^2 = 8.42$, df 1, $p=0.0037$) and not from 15-24 year old women (Table 1).

For the 1994 anonymous seroprevalence survey, 14,780 prenatal blood samples were analyzed, corresponding to a population of whom 28% were 15-24, 60% were 25-34, and 12% were 35-44 years of age (Table 2). Fifty-one percent resided in the Lower Mainland,

and 49% were from other BC locations. The HCV seroprevalence rate was 135/14,780 (0.9%), or 91.3/10,000 (95% CI 76.9-108.4). The rate of reported HCV among pregnant women calculated from the 2000-2002 study dataset was 44% less than the rate determined from the 1994 anonymous survey: 50.3/10,000 vs. 91.3/10,000 ($p < 0.0001$) respectively (Table 2). This difference was most pronounced in the Lower Mainland; 101.3/10,000 vs. 48.7/10,000 ($p < 0.001$).

DISCUSSION

The rate of reported HCV among pregnant women in BC was 50.3/10,000 (0.5%). To date, similar studies have not been performed in other Canadian provinces, but our results are comparable to reported prevalence rates for pregnant and postpartum women in other developed countries, such as Switzerland (0.7%) and England (0.8%),^(9,10) and lower than reported rates in Italy (2.4%)¹¹ and parts of the United States (2.3-4.4%).^{12,13}

Explanations for geographical patterns observed in HCV testing and prevalence rates must consider both factors that influence HCV reporting and actual HCV prevalence. Differences between BC regions may be related to varying physician test ordering practices, care-seeking and disclosure behaviours of pregnant women, or factors that are related to HCV risk. Reported rates were highest in the northern region of BC (Northern Health Authority, 0.66%), which may be due to increasing rates of injection drug use (IDU) in northern communities,¹⁴ or the higher proportion of Aboriginal women residing in northern regions who appear to be at greater risk of HCV infection, in part because they are over-represented in groups practising high-risk behaviours.^{15,16} In contrast, we found that HCV prevalence was lowest in the populous suburban region southwest of Vancouver (Fraser HA; 0.38%). This was contrary to BC CDC surveillance reports from this time period which indicated that one third of HCV cases were located in Fraser Health,¹⁷ although of note, several correctional facilities are located in this region and may in part drive the higher reported rates.¹⁸ Regardless, this discrepancy is concerning as it may reflect low rates of testing of pregnant women and under-reporting in this region. Alternatively, the relatively low proportion of HCV cases in pregnancy detected in Fraser Health may reflect ethnocultural barriers to prenatal screening for infectious diseases, as approximately 30% of the population self-identify as non-Caucasian (predominantly of South Asian, Asian and Aboriginal descent),¹⁹ or differential fertility rates in low vs. high HCV-prevalence subpopulations.

We found that reported prevalence was significantly higher among women aged 35-44 (0.62%) than women aged 25-34 (0.46%). This is consistent with previous population-based studies and most likely reflects the cumulative effect of risk behaviours over time.²⁰ Furthermore, there was evidence that reported HCV prevalence was higher among young women aged 15-24 (0.54%) than among women aged 25-34, both within Health Authorities and across the province. The highest prevalence rate across all regional and age categories was among young women residing in Northern BC (0.82%), raising concern that this population may be particularly vulnerable to HCV infection. However, due to a comparatively small sample size and higher rates of HCV testing within the 15-24 age category, these results should be interpreted with caution and further study is warranted.

A limitation of this study was that only 20% of the pregnant population had been tested for HCV. Of these, 2.5% were anti-HCV

reactive, yielding an overall 0.5% prevalence rate for this study population. However, this represents the minimum actual prevalence of HCV, as the remaining 80% may have included women infected with HCV but unaware of their status. Furthermore, risk factor profiles were not available and it was not known if the women who were tested had more recognized or self-reported risk factors than women not tested.

This uncertainty was initially what prompted the comparison of study results to the 1994 anonymous seroprevalence survey. This comparison suggested that the public health-reported HCV prevalence may underestimate the true prevalence rate among pregnant women. There are approximately 40,000 deliveries in BC each year; the prevalence rate of 0.5% calculated in this study suggests that 200 of these women are known to be HCV positive. However, the anonymous seroprevalence survey indicated the true prevalence rate may be as high as 0.9%, meaning that an additional 160 pregnant women with HCV infection may remain undetected. The vertical transmission rate of HCV is approximately 5%, suggesting that as many as 8 infants may be infected with HCV each year.

There are several possible explanations for the discrepancy in reported versus anonymously detected HCV prevalence. Studies have shown that between 40-75% of HCV-infected pregnant women do not report HCV risk factors.²¹⁻²⁴ Risk-based prenatal screening may also fail to identify many HCV-infected women due to detection, diagnostic, testing and recall biases, along with reporting bias related to patient disclosure. Pregnant women in particular may be unlikely to disclose past injection drug use (IDU), the self-reported route of transmission for about 70-80% of HCV cases in Canada.²⁵ Further complicating the issue is that hepatitis C infection is a slowly progressing disease, and infected persons can remain asymptomatic up to 20 years after exposure.⁴

Alternatively, the possibility that the two populations are not comparable must be considered. Ideally, a contemporary age- and geographically-matched anonymous survey would be used to extrapolate the reported versus true burden of HCV among pregnant women in BC. For our purposes, the most recent data available were from the anonymous survey, which had been conducted 6-8 years prior on a population that differed in age and geographic distribution. Neither study was designed to identify specific factors or subgroups that may have contributed to HCV prevalence rates. However, there are several external factors that suggest that by 2000-2002, we could expect that HCV testing and reporting would have increased, thus facilitating identification of HCV-positive persons relative to 1994. This includes the launch of provincial "track-back" programs to identify persons infected through contaminated blood products in 1996, the introduction of more sensitive and accurate laboratory tests for HCV in 1997, and the federal compensation program approved in 2001. Taken together, these factors should have improved uptake of HCV testing and detection of HCV infection in 2000, particularly among those considered "high risk". Furthermore, the number of new cases of HCV diagnosed in BC has more than doubled from 1994 (52/100,000) to 2000-2002 (108/100,000).²⁶ Therefore, it is plausible that HCV could be under-detected and -reported in pregnant women: our data show consistently higher rates among pregnant women in the anonymous survey versus the study population, across different age and geographic strata, underscoring the need for further research in this area.

Our results emphasize that until a more comprehensive strategy for the prevention and management of HCV infection in pregnancy is implemented in Canada, health care professionals should routinely obtain a history of migration and/or travel, illegal drug use and high-risk sexual practices to identify women who would benefit from testing and counseling. Further evaluation of the impact of the current risk-based prenatal HCV screening policy is warranted, incorporating comparison to more comprehensive prenatal anti-HCV screening as a cost-effective public health secondary prevention strategy in BC. This would achieve early recognition of disease in the younger female population, permitting more effective treatment interventions for the mother, and testing, preventive care and treatment for the infant.

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RÉSUMÉ

Contexte : Bien que les infections par le virus de l'hépatite C (VHC) soient relativement courantes au Canada, tout particulièrement en Colombie-Britannique (C.-B.), on manque d'information sur la prévalence réelle du VHC chez les femmes enceintes. À l'heure actuelle, les femmes enceintes ne sont dépistées que si elles correspondent aux critères de risques, ce qui peut entraîner une sous-détection du VHC dans cette population. Le but de notre étude était de déterminer le taux de prévalence global, l'âge et la répartition géographique des cas d'infection à VHC déclarés chez les femmes enceintes en C.-B., et de comparer ces résultats à ceux d'une enquête anonyme sur la séroprévalence du VHC menée antérieurement.

Méthode : Nous avons déterminé la prévalence du VHC déclaré par un maillage confidentiel des résultats de dépistage prénatal de la base de données de la Société canadienne du sang avec les résultats des tests de sérodiagnostic du VHC effectués par les laboratoires provinciaux de mai 2000 à octobre 2002. Les données ont été stratifiées selon le groupe d'âge et le lieu géographique, puis comparées à celles d'une enquête anonyme sur la séroprévalence prénatale datant de 1994.

Résultats : Le taux de prévalence global du VHC était de 50,3 p. 10 000 (IC de 95 % = 46,3-54,6), soit 0,5 % de la cohorte. La plus forte prévalence a été observée dans la région Nord de la C.-B. (66,2/10 000, IC de 95 % = 51,4-85,3), et la plus faible dans la populeuse région suburbaine du Sud-Ouest de Vancouver (38/10 000, IC de 95 % = 32,3-44,8). N.B. : Le taux de VHC déclaré chez les femmes enceintes était significativement inférieur au taux de séroprévalence anonyme : 50,3/10 000 contre 91,3/10 000 ($p < 0,0001$).

Conclusion : Les taux de VHC déclaré, chez les femmes enceintes, étaient inférieurs d'environ la moitié aux taux observés dans l'enquête de séroprévalence anonyme. Il faudrait pousser la recherche pour déterminer l'utilité respective de la politique de dépistage sélectif actuellement en vigueur et d'un dépistage prénatal universel du VHC pendant la grossesse.

Mots clés : hépatite C; grossesse; transmission mère-enfant; dépistage prénatal