Outcomes of infectious syphilis in pregnant patients and maternal factors associated with congenital syphilis diagnosis, Alberta, 2017–2020

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Abstract

Background: Congenital syphilis (CS) is a significant public health challenge, requiring early diagnosis and treatment to improve infant outcomes. The aim of this study is to describe public health outcomes of infectious syphilis cases among pregnant patients and factors associated with a CS diagnosis for their infant.

Methods: We conducted a retrospective review of demographic and clinical characteristics of infectious syphilis cases diagnosed during pregnancy and resulting infant outcomes in Alberta from 2017 to 2020 from the provincial communicable disease database. Adequate maternal treatment was defined as receiving at least one dose of Benzathine penicillin G-LA 2.4 million units IM at least 28 days before delivery. Univariate and multivariate analysis was performed to determine factors associated with CS diagnosis using SPSS version 25.

Results: A total of 374 cases of infectious syphilis were diagnosed in pregnancy, with two patients being diagnosed twice in a single pregnancy. The majority (79.1%; n=296) of women had a live birth, followed by therapeutic abortion (9.4%; n=35), stillbirth (7.5%; n=28) and spontaneous abortion (4.0%; n=15). Infant records (n=265) were available for review (n=117 CS cases and 148 non-cases). Correlates associated with CS were screening time in third trimester (adjusted odds ratio [AOR] 8.4, 95% confidence interval [CI], 2.9–24.6) and fewer than 28 days before delivery (AOR 8.1, 1.4–47.8 [vs. first and second trimester] and inadequate treatment (AOR 86.1, CI, 15.9–466.5). Among the CS cases, 23.1% (n=27) were stillborn compared with one (0.7%) stillbirth in the non-CS infants (p<0.001).

Conclusion: The early identification and treatment of syphilis in pregnancy is crucial to preventing poor infant outcomes.

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Introduction

Congenital syphilis (CS) is a worldwide public health challenge and reflects the incidence of infectious syphilis in the heterosexual female population (1). Untreated syphilis during pregnancy can profoundly affect pregnancy outcomes, resulting in spontaneous abortion, stillbirth, perinatal death and serious sequelae in infected infants.

The World Health Organization has set global targets for 2030 to reduce the incidence of syphilis by 90% and to reduce CS to 50 or fewer cases per 100,000 live births in 80% of countries (2). The estimated global CS rate in 2016 was 473 (range=385–561) per 100,000 live births and 661,000 (range=538,000–784,000) total CS cases (3).

A provincial syphilis outbreak was declared in Alberta in 2016, after rates of infection doubled from 3.9/100,000 in 2014 to 8.8/100,000 in 2015 and have climbed to 56.7/100,000 in 2020. During this time, the rate among women has increased 90-fold

from 0.6/100,000 in 2014 to 49.6/100,000 in 2020 (4). The proportion of pregnant cases climbed from 0% in 2014 to 15% in 2020 (*unpublished data*). From 2012 to 2016, only a single CS case had been reported compared with 121 CS cases reported from 2017 to 2020, with 45 and 56 cases diagnosed in 2019 and 2020, respectively (4). Twenty-eight infants were stillborn during this time.

The aim of this study is to describe the epidemiology of infectious syphilis cases diagnosed during pregnancy and to report pregnancy and neonatal outcomes.

Methods

A retrospective review was conducted of demographic and clinical characteristics of infectious syphilis cases diagnosed during pregnancy and resulting pregnancy and neonatal outcomes in Alberta (current population 4.3 million) from 2017 to 2020. In Alberta, prenatal syphilis screening is universally recommended during the first trimester, at delivery, and throughout pregnancy for those with ongoing risk (5,6). All cases of syphilis are reportable by laboratories and clinicians to the provincial sexually transmitted infections (STI) program that is responsible for ensuring adequate treatment and partner notification of all confirmed cases. Partner notification nurses (PNN) act as case managers for patients by collaborating with the patient, the testing and treating healthcare providers, and the STI medical consultant to facilitate appropriate assessment, treatment and follow-up of patients and their sexual partners. All patients are assessed for pregnancy through patient or healthcare provider interviews by the PNN. For pregnant patients, the PNN also coordinates care with the delivery site to ensure serology at delivery and appropriate follow-up of infants.

Sexually transmitted infections medical consultants completed maternal staging of syphilis according to provincial case definitions (7) and reviewed infants for possible diagnoses with CS.

De-identified data were extracted from the provincial communicable disease database on June 25, 2021; mothers and infants were linked by unique record numbers. Variables extracted for each syphilis case included demographic, behavioural and clinical factors. Ethnicity, history of transactional sex, injection drug use (IDU), sex with a person who injects drugs (PWID) were self-reported during PNN interviews as part of routine public health follow-up and reporting requirements. A symptom inquiry for sores, rashes, lesions and neurological signs was completed through client self-report or by the healthcare provider. Correctional involvement included any case where the patient was initially diagnosed or treated in a correctional facility. Alberta is split into five geographic zones and these zones were assigned based on the patient's postal code. Healthcare proximity was defined based on population density and travel times to health services: metro/urban (municipalities with a population density of at least 20,000 per km2 and their adjacent communities with a tertiary or regional hospital); rural (population density between 100–10,000 per km2); and rural remote (population density fewer than 100 per km2 and more than 200 km to a regional centre). Public health contact was defined as patients contacted by PNN versus patients who PNN were unable to contact. Screening time was the difference between the delivery date and the collection date of the first positive specimen and then stratified into three categories: first and second trimester (at least 91 days); third trimester (28–90 days), and fewer than 28 days prior to delivery as this timing was insufficient for adequate treatment. Adequate maternal treatment was defined as receiving at least one dose of Benzathine penicillin G-LA 2.4 million units IM or aqueous crystalline penicillin G 18-24 million units per day for at least 10 days and more than 28 days before delivery. Time to treatment was calculated from the date of the first positive test result to the initial dose of medication. For birth outcomes, stillbirth was defined as a fetal death after 20 weeks gestation and spontaneous abortion was fetal demise at or before 20 weeks gestation.

Descriptive analyses were completed for IDU, sex with a PWID and transactional sex; however, due to large proportions of missing data (25%–31%), these variables were excluded from additional analysis. To identify factors associated with CS, analyses were performed by comparing CS and non-CS cases. Univariate analyses were performed using Chi-square or Fisher's exact test for categorical variables and Mann-Whitney tests for continuous variables, excluding missing data. To identify independent factors associated with CS, multivariable logistic regression was performed. All variables significant at $p \leq 0.10$ at the univariate level were assessed for multicollinearity. The number of days to treatment and adequate treatment were found to be highly correlated, so number of days to treatment was not included in model building. Models were built using all significant variables and forward step-wise approach was found to have the best Hosmer-Lemeshow Goodness-of-Fit score. Analyses were completed using IBM SPSS Statistics 19 (IBM, Armonk, New York, United States).

Results

A total of 374 cases of infectious syphilis were diagnosed in pregnancy between January 1, 2017 and December 31, 2020, with two patients being reinfected during the same pregnancy. The majority of cases self-reported First Nations ethnicity, resided in the Edmonton zone, were from a metropolitan/urban area, were diagnosed with early latent syphilis, were contacted by a PNN, and had a live birth. All cases were HIV-negative. A significant proportion of women reported IDU (21.0%; n=58/276), sex with a PWID (18.1%; n=47/259), and transactional sex (11.0%; n=31/281); however, these variables had high proportions of missing data (**Table 1**).

Table 1: Maternal characteristics of infectious syphilis cases among pregnant patients in Alberta, 2017–2020 (N=374)

Characteristics	N=374	%[a]
Median age at diagnosis (years, IQR)	26	22–30
Ethnicity		
White	58	15.5
First Nations	228	61.0
Métis	36	9.6
Other	6	1.6
Unknown/missing	46	12.3
Correctional facility		
No	342	91.4
Yes	32	8.6
Geographic zone		
South	2	0.5
Calgary	16	4.3
Central	30	8.0
Edmonton	217	58.0
North	109	29.1
Healthcare proximity		
Metro/urban	229	61.2
Rural	103	27.5
Rural remote	42	11.2
Diagnosis year		
2017	15	4.0
2018	66	17.6
2019	145	38.8
2020	148	39.6
Public health contact		
Client contacted	325	86.9
Unable to contact	49	13.1
Syphilis stage		
Primary	114	30.5
Secondary	21	5.6
Early latent	238	63.6
Early neurosyphilis	1	0.3
Median days to treatment[b] (IQR)	6	3–13
Birth outcome		
Live birth	296	79.1
Stillbirth	28	7.5
Spontaneous abortion	15	4.0
Therapeutic abortion	35	9.4

Abbreviation: IQR, interquartile range
[a] This table represents 374 cases of infectious syphilis among 372 pregnancies: two patients were reinfected during the same pregnancy
[b] Five cases had no treatment record at time of diagnosis

Of the 324 cases with a live birth or stillbirth, infant records were available for all but three cases. Seven sets of twins were born, resulting in a total of 328 infant records for review. Nearly one-third (35.7%; n=117) of the infants were diagnosed with CS, 45.1% (n=148) of infants did not meet CS case definitions (non-CS) and 19.2% (n=63) of infants remain unstaged and are continuing follow-up. Maternal characteristics associated with CS in univariate analysis were no contact with PNN, having two or more partners in the last year, screening time in third trimester or fewer than 28 days before delivery, and not receiving adequate treatment (**Table 2** and **Table 3**). Of the total 265 cases, one-third (35.8%; n=95) of cases were screened less than a month before delivery, with many of these (25.3%; n=67) being within two days of delivery. The majority (61.1%; n=162) of patients received adequate treatment for the prevention of CS; 161 patients received Benzathine penicillin G-LA 2.4 million units IM at least 28 days prior to delivery and one patient received aqueous crystalline penicillin G 24 million units per day for 14 days. The remaining 39.2% (n=104) of patients were not treated adequately. One-quarter (24.5%; n=65) of patients were treated with at least a single dose of Benzathine penicillin G-LA 2.4 million units IM at or post-delivery, 11.3% (n=30) were treated 1–27 days prior to delivery, two (0.8%) cases received doxycycline 100 mg b.i.d. for 14 days post-delivery, and one case received insufficient treatment with aqueous crystalline penicillin G 5 million units intravenously in a single dose post-delivery. An additional five cases (1.9%) had no treatment record at the time of analysis. Correlates that remained independently associated with CS upon multivariable analysis were screening time in third trimester (adjusted odds ratio [AOR] 8.4, 95% confidence interval [CI], 2.9–24.6) and fewer than 28 days before delivery (AOR 8.1, 1.4–47.8 [vs. first and second trimester], and inadequate treatment (AOR 86.1, CI, 15.9–466.5). Among the CS cases, 23.1% (n=27/117) were stillborn compared with one (0.7%) stillbirth in the non-CS infants ($p<0.001$). Despite diagnosis during the first and second trimester of nine CS cases, four cases were treated within fewer than 28 days before delivery. Of the 237 live births, all CS cases received treatment. Thirty (20.4%) of the non-CS cases also received treatment; these cases did not meet Alberta case definition for CS (8) but were treated at the time of delivery based on clinical judgement and maternal history known at the time of admission after assessment by paediatric Infectious Diseases specialists.

Table 2: Univariate analysis of maternal characteristics associated with infant outcomes from infectious syphilis cases among pregnant patients in Alberta, 2017–2020 (N=265)

Maternal characteristics	Congenital		Non-cases		Total		*p*-value	Unadjusted OR	
	(n=117)	%	(n=148)	%	(N=265)	%		Rate	95% CI
Median age at diagnosis (years, IQR)	27	23–31	26	21–30	26	22–31	0.18	1.0	1.0–1.1
Ethnicity									
White	17	14.5	24	16.2	41	15.5	0.37	Ref	Ref
First Nations	71	60.7	96	64.9	167	63.0	-	1.0	0.5–2.1
Métis	13	11.1	7	4.7	20	7.5	-	2.6	0.9–8.0
Other	1	0.9	3	2.0	4	1.5	-	0.5	0.1–4.9
Unknown/missing	15	12.8	18	12.2	33	12.5	-	1.2	0.5–3.0
Correctional facility									
No	107	91.5	133	89.9	240	90.6	0.66	Ref	Ref
Yes	10	8.5	15	10.1	25	9.4	-	0.8	0.4–1.9
Geographic zone									
Calgary	4	3.4	5	3.4	9	3.4	0.05	Ref	Ref
Central	16	13.7	6	4.1	22	8.3	-	3.3	0.7–16.7
Edmonton	63	53.8	90	60.8	153	57.7	-	0.9	0.2–3.4
North	34	29.1	47	31.8	81	30.6	-	0.9	0.2–3.6
Healthcare proximity									
Metro/urban	65	55.6	93	62.8	158	59.6	0.09	Ref	Ref
Rural	39	33.3	32	21.6	71	26.8	-	1.7	1.0–3.1
Rural remote	13	11.1	23	15.5	36	13.6	-	0.8	0.4–1.7
Diagnosis year									
2017	5	4.3	9	6.1	14	5.3	0.01	1.6	1.2–2.1
2018	16	13.7	43	29.1	59	22.3	-	-	-
2019	44	37.6	52	35.1	96	36.2	-	-	-
2020	52	44.4	44	29.7	96	36.2	-	-	-
Public health contact									
Client contacted	89	76.1	136	91.9	225	84.9	<0.001	Ref	Ref
Unable to contact	28	23.9	12	8.1	40	15.1	-	3.6	1.7–7.4
Symptoms[a]									
No	49	48.0	64	44.8	113	46.1	0.61	Ref	Ref
Yes	53	52.0	79	55.2	132	53.9	-	0.9	0.5–1.5
Number of partners in last 12 months									
Fewer than 2	21	17.9	10	6.8	31	11.7	0.005	Ref	Ref
At least 2	96	82.1	138	93.2	234	88.3	-	0.3	0.2–0.7
Maternal syphilis stage									
Primary	34	29.1	43	29.1	77	29.1	1.00	1.0	0.6–1.7
Secondary	8	6.8	9	6.1	17	6.4	-	1.1	0.4–3.2
Early latent	75	64.1	95	64.2	170	64.2	-	Ref	Ref
Early neurosyphilis	0	0	1	0.7	1	0.4	-	-	0 cell precluded regression analysis
Median days to treatment[b]	5	2.0–8.5	6	3.0–10.0	6	3.0–10.0	0.03	1.0	0.999–1.01

Table 2: Univariate analysis of maternal characteristics associated with infant outcomes from infectious syphilis cases among pregnant patients in Alberta, 2017–2020 (N=265) (*continued*)

Maternal characteristics	Congenital		Non-cases		Total		*p*-value	Unadjusted OR	
	(n=117)	%	(n=148)	%	(N=265)	%		Rate	95% CI
Screening time									
First to second trimester	9	7.7	111	75.0	120	45.3	<0.001	Ref	Ref
Third trimester	18	15.4	32	21.6	50	18.9	-	6.9	2.8–16.9
At least 28 days from delivery	90	76.9	5	3.4	95	35.8	-	222	71.9–685.9
Adequate treatment									
No	99	84.6	4	2.7	103	38.9	<0.001	198.0	65.0–602.7
Yes	18	15.4	144	97.3	162	61.1	-	Ref	Ref

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; Ref, reference; -, no applicable
[a] Excludes 20 cases with missing data
[b] Excludes six cases with missing treatment date

Table 3: Multivariate analysis of maternal characteristics associated with infant outcomes from infectious syphilis cases among pregnant patients in Alberta, 2017–2020 (N=265)

Maternal characteristics	Adjusted OR	95% CI	*p*-value
Screening time			
First to second trimester	Ref	-	-
Third trimester	8.4	2.9–24.6	<0.001
At least 28 days from delivery	8.1	1.4–47.8	0.02
Adequate treatment			
Yes	Ref	-	-
No	86.1	15.9–466.5	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference; -, no applicable

Discussion

In Canada, the rates of infectious syphilis have been increasing sharply in the past five years; particularly alarming is an increase of infectious cases by 740% among females between 2016 and 2020 (8). Similar epidemiological trends have been seen in the United States with nearly 2,100 cases of CS in 2020 (9). Since the current syphilis outbreak started in 2015, Alberta has seen an unprecedented number of infectious syphilis cases among pregnant women resulting in CS cases and stillbirths. Inadequate maternal treatment was the most important predictor for a diagnosis of CS in our study. Several factors contributed to inadequate treatment during pregnancy. Firstly, the odds of giving birth to an infant with CS were eight times higher among patients screened in the third trimester and for patients screened in the last month of pregnancy as the late diagnosis leaves inadequate time for treatment. Furthermore, four of the nine CS cases with maternal screening during the first and second trimesters did not receive treatment four weeks prior to delivery due to barriers to care. Our findings are similar to those in a recent study on maternal syphilis treatment that showed that no pregnant patient with treatment in the first trimester delivered a neonatal CS case. Patients who initiated treatment in the third trimester had an increased risk of stillbirth, preterm birth and low birth weight (10). Another study examining the determinants associated with CS and adverse pregnancy outcomes found that every week of delay in treatment was related to 2.82-fold increased risk for adverse pregnancy outcomes (11).

While screening in the first trimester and at mid-gestation aims at preventing CS, the goal of screening at delivery is early diagnosis and treatment of infants born to mothers with infectious syphilis. A cost effectiveness analysis in the United States in 2018 found that repeat screening in the third trimester is superior to single screening during the first trimester and is both cost-effective and results in improvement in maternal and neonatal outcomes (12). During the last infectious syphilis outbreak in Alberta in the mid-2000s, universal mid-gestation screening was introduced but, after a review of the Alberta prenatal screening program, it was discontinued in 2012 due to low uptake and limited utility for the diagnosis of additional new syphilis infections (13), although syphilis rates were lower at that time. Canadian and United States Centers for Disease Control and Prevention (CDC) syphilis screening guidelines recommend screening in the first trimester or at the first prenatal visit and repeat screening at 28–32 weeks' gestation and again at delivery for patients in areas with high rates of syphilis and for women at ongoing risk for syphilis acquisition (14,15). Our study results support current Alberta syphilis screening guidelines for pregnant patients recommending universal maternal screening in the first trimester, at delivery (5,6) and rescreening for those at ongoing risk. The majority of the mothers interviewed reported multiple partners in the last year and more than one-half reported symptoms, thereby meeting current recommendations for rescreening during pregnancy. Despite meeting current provincial screening recommendations for being at risk and requiring frequent re-screening throughout pregnancy, we found a high number of patients with an initial screen late in pregnancy (one-quarter within two days of delivery) and two cases of reinfection during the same pregnancy. We believe that frequent

testing and re-testing of pregnant women up to monthly after an initial negative test result but who are at ongoing risk is an important tool to prevent further newborn syphilis cases. Increasing overall knowledge on syphilis and awareness of existing screening guidelines among medical providers are important steps to improve health outcomes of pregnant women and their infants. Opportunistic screening when women at risk present to healthcare for non-pregnancy related causes can lead to earlier diagnosis and treatment thereby reducing morbidity and mortality related to CS. Use of point of care testing and symptomatic syphilis treatment should be considered for women at risk for being lost to follow up. Offering screening to women in non-traditional care settings, such as addiction treatment centers, correctional facilities or emergency room departments, can further increase screening among women otherwise not engaging in prenatal care. The high proportion of cases in our study diagnosed in the third trimester underlines the need for non-traditional approaches for testing and treatment, as many patients who access services late in pregnancy are affected by adverse social determinants of health including poverty and mental health and addictions issues. In addition, a significant proportion of patients were Indigenous, demonstrating the need for culturally appropriate services. In response to the mid-2000s resurgence of infectious syphilis in Alberta, an outreach team in Edmonton geographical zone expanded to include registered nurses with the team of Indigenous community health representatives; offering culturally appropriate care. Outreach services can be a valuable strategy in reaching persons at risk for STIs since services are delivered to populations that would not normally be aware of or able to access services due to their life circumstances (16). Previous evaluations of outreach services in Edmonton, including the use of incentives, have highlighted the utility of these services in identifying new cases (17).

Nurse case management has been found to increase linkage to care and improve patient outcomes (18,19). In our study population, patients without public health contact had worse outcomes with a 3.6-fold increased risk of giving birth to an infant with CS. Overall, the median time from first specimen collection to initiating treatment was six days and only five cases remained untreated. We hypothesize that our treatment success is related to the case management role that PNNs play in client engagement and prioritization of pregnant patients and their sexual contacts.

Limitations

This is the first Canadian study describing outcomes of infants born to patients with infectious syphilis during pregnancy. One possible limitation of our study is that our reported cases may underestimate the number of pregnant patients with syphilis, especially with the reduction of health services and patients choosing not to access care during the coronavirus disease 2019 pandemic, as well as cases that PNNs were unable to contact. Additionally, since we used retrospective data collected for surveillance purposes, data on behavioural characteristics, like IDU and transactional sex, was missing in a significant proportion of our study population, which may be related to underlying stigma and social desirability bias, and therefore underestimate their impact.

Conclusion

Our study shows that early identification of syphilis in pregnancy through adherence to prenatal screening guidelines and a strong public health program to link patients to timely care are key in the prevention of CS cases. As syphilis rates increase and infections spread to rural and remote areas with limited access to health and social programs, it is imperative that sufficient resources for public health follow-up are available to facilitate the engagement of patients in care. In addition, a review of current screening practices in combination with increased awareness not only among members of the healthcare team but also in the general public may be required to respond to the changing epidemiology of syphilis, particularly to the increased prevalence of syphilis in young heterosexual populations. Lastly, we need to continue to engage with and work with affected communities to deliver services in a culturally and societally appropriate way.

Authors' statement

JG — Contributed to the concept of this report, performed statistical analysis, contributed to acquisition of data, contributed to interpretation of data, revising the manuscript critically for important intellectual content, and approved the final version
PS — Contributed to the concept of this report, drafted the initial manuscript, contributed to interpretation of data, revising the manuscript critically for important intellectual content, and approved the final version
JK — Contributed to acquisition of data
LE, LB, AES, AC — Contributed to interpretation of data, revising the manuscript critically for important intellectual content, and approved the final version

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Competing interests

None.

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