Surveillance PROTOCOL

(British Columbia Sub-Protocol)

Canadian COVID-19 in Pregnancy Surveillance:
Epidemiology, Maternal and Infant Outcomes

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SUMMARY

Title	Canadian COVID-19 in Pregnancy Surveillance: Epidemiology and Maternal and Infant Outcomes
Goal	To provide BC data on COVID in pregnancy to the Canadian Surveillance to support clinical care and public policy.
Objectives	1. By way of contributing BC data, facilitate determination of the burden of SARS-CoV-2 infection in pregnancy in Canada 2. To capture and report maternal outcomes, including degree of respiratory illness and requirement for hospitalization and/or ventilation support 3. To determine fetal and infant outcomes including evidence of transmission of maternal SARS-CoV-2 infection to the infant 4. To provide data to facilitate planning and support for COVID-19 affected pregnancies in the Canadian context 5. To contribute data to international collaborations, allowing for optimized international understanding of COVID-19 in pregnancy
Timeline	April 2020-December 2023, to be adjusted based on Canadian and global epidemiology
Project design	Prospective Observational / Surveillance Cohort
Inclusion criteria	• Pregnant or recently delivered • Living in Canada • Documented SARS-COV-2 infection in pregnancy
Data collection and time points	• At time of first referral to provincial surveillance • At time of delivery or termination of pregnancy • At 6-8 week postpartum follow-up for both maternal and infant data collection • Optional longer follow up for infants

BACKGROUND

1.1 EPIDEMIOLOGY OF SARS-COV-2

In December 2019, a novel coronavirus, eventually termed Severe Acute Respiratory Syndrome associated Coronavirus-2 (SARS-CoV-2) was identified in Wuhan, China. On March 11, 2020, the WHO declared Coronavirus Disease 19 (COVID-19), the respiratory illness caused by SARS-CoV-2 infection, an official global pandemic. As of April 8, 2020, globally, SARS-CoV-2 has infected >1,500,000 people and caused over 88,000 deaths.[1] As of April 8, 2020, Canada has 19,289 confirmed cases and 435 deaths, with cases occurring in individuals returning from international travel or their close contacts and via extensive community spread.[2]

Given that pneumonia is a significant cause of maternal morbidity and the leading cause of fatal non-obstetric infection in pregnant women, the global spread of SARS-CoV-2 raises unique questions and significant concerns for the health of pregnant women and their fetuses. Pregnant women and their families are looking to prenatal care providers for information on risks and guidance on how to prevent transmission and manage infection with SARS-CoV-2. Globally, there is a dearth of data on SARS-CoV-2 to inform recommendations for pregnant women and their care providers. We propose a Canadian surveillance program to better understand COVID-19 in pregnancy, to increase understanding of the epidemiology of COVID-19 in pregnancy, and to provide critical data to inform recommendations for pregnant women and their infants.

1.2 RESPIRATORY INFECTIONS IN PREGNANCY

Due to physiological and immunological changes during pregnancy, pregnant women exhibit greater predisposition and susceptibility to some infections. Pregnant women with lower respiratory tract infection often have more severe illness, and have higher rates of admission to hospital and intensive care compared to non-pregnant counterparts.[3] Recognizing there are very limited data on SARS-CoV-2 in pregnancy, we look to experience with other respiratory illnesses to help guide clinical management, while simultaneously seeking to rapidly acquire quality data specific to SARS-CoV-2.

There have been two other large outbreaks of highly pathogenic coronaviruses that have had global implications in the past two decades: Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS). Although these viruses do not mirror our initial understanding of SARS-CoV-2 in terms of genetic structure or clinical manifestations, they provide insight with respect to the potential impacts of SARS-CoV-2 on pregnant women. Published reports of SARS and MERS in pregnant women are limited to a small body of case reports and case series.[4-9] From these limited reports, we know that a high proportion of pregnant women with SARS and MERS suffered severe illness and required intensive care and cardiorespiratory support. Importantly, cases of maternal death have been associated with SARS and MERS infection. Only one case-control study assessed SARS outcomes in pregnant women compared to non-pregnant women, demonstrating that pregnant women with SARS had worse outcomes than similarly aged non-pregnant women.[10]

Fetal-infant health is a unique and critical consideration for the care of pregnant women. Reports on the impact of SARS and MERS on pregnancy outcomes provide varied findings. Among women affected by SARS and MERS during the first trimester, outcomes include spontaneous abortion.[4] Reports of pregnancies affected by SARS and MERS during the second and third trimester, include

stillbirth, intrauterine growth restriction, and preterm birth.[4,9] In contrast to these adverse outcomes, a number of pregnancies had no adverse outcomes despite maternal infection with SARS or MERS.[6-8] Broadly speaking and drawing upon available evidence and knowledge of other respiratory disease in pregnancy, severity of respiratory compromise is likely the best predictor of adverse pregnancy outcomes.

1.3 SARS-CoV-2 IN PREGNANCY

Data on the impact of SARS-CoV-2 in pregnancy has been limited in the published literature. As of April 9, 2020, there were 24 publications in the literature that contained original case data for pregnancy outcomes.[11-34] It appears that there were many redundant case reports, so we have ascertained that there appears to be 126 unique cases described in the published literature.

The general pregnancy outcomes, demonstrate that there were 87 women who have delivered in the course of these study description and 39 whose pregnancy was not completed at the time of publication. Hence there are 89 neonates born to 87 women (2 sets of twins), from which to draw conclusions. Of these, 75% were born via caesarian section – this is related to the preponderance of data from China where their policy was to primarily deliver by caesarian section. Notably, 36.6% (n=26) delivered preterm (<37 weeks gestational age), of which, 21.1% were late preterm (34-36+6 weeks), 9.9% were less than 34 weeks and 5.6% were born preterm with no exact gestational age reported. The infant outcomes reveal that 25.9% (n=14) were low birth weight (<2500g).

Vertical transmission of SARS-CoV-2 has been greatly debated. In this review of the literature, there were 76.4% of cases with at least some infant testing and outcome information. Overall, 91.2% of cases showed no evidence of vertical transmission and there were 6 cases where evidence was equivocal. 5.9% (n=4) of neonates had positive nasopharyngeal or throat swabs, however postnatal transmission via droplet or contact exposure cannot be ruled out in the hospital environment for these cases. Other types of testing revealed that 13.8% (n=12) had umbilical cord blood tested for SARS-CoV-2 and all were negative, 12.6% (n=11) had amniotic fluid tested for SARS-CoV-2 and all were negative, 12.6% (n=11) had breast milk tested for SARS-CoV-2 and all were negative, 10.3% (n=9) had placental testing for SARS-CoV-2 and all were negative, 3.4% (n=3) had vaginal secretions tested for SARS-CoV-2 and all were negative.

Adverse neonatal outcomes were primarily related to prematurity. Other serious adverse outcomes such as birth asphyxia, stillbirth, and neonatal death were rare among all neonates. These adverse outcomes are not necessarily attributed to SARS-CoV-2 exposure. Three specific cases are of particular interest:

1) One infant [32] was born via Caesarean section for fetal distress at 31+2 weeks, birth weight of 1580 g, and Apgars of 3, 4, and 5 at one, five and ten minutes. Neonatal respiratory distress syndrome and pneumonia were confirmed by chest x-ray on NICU admission and resolved by Day of Life 14 with non-invasive ventilation, caffeine, and antibiotics. This infant also had suspected sepsis with an *Enterobacter*-positive blood culture, which resolved with treatment. This infant also had positive nasopharyngeal and anal swabs for SARS-CoV-2 on Day of Life 2 and 4, which was repeated and negative by Day of Life 7. It is difficult to establish an association for this infant's health status with SARS-CoV-2 infection given the confounding issues of prematurity, asphyxia, and bacterial sepsis.

2) In 1/89 neonates (1.1%) was a stillbirth.[25] Delivery was via Caesarean section at approximately 34 weeks. Although there was no underlying medical disease, this pregnant patient became critically ill with COVID-19 and their condition deteriorated during hospitalization. The patient required ICU

admission and had multiple organ dysfunction syndrome (MODS), including: ARDS requiring intubation and mechanical ventilation, acute hepatic failure, acute renal failure, and septic shock. This patient was still on ECMO support at the conclusion of the study. The study only reports that no evidence of vertical transmission of SARS-CoV-2 was found, but details regarding the specifics of infant or other testing are not provided.
3) In 1/89 neonates (1.1%) was a neonatal death.[34] This infant was born via Caesarean section at 34+5 weeks, birth weight 2200 g, and Apgars of 8 and 8 at one and five minutes. About 30 minutes after birth, the infant developed shortness of breath and moaning, so was admitted to NICU. At 8 days of life, the infant developed refractory shock, multiple organ failure, and DIC from gastric bleeding. In spite of transfusion and resuscitation efforts the infant unfortunately died on Day of Life 9. The infant had a negative throat swab for SARS-CoV-2. The mother's COVID-19 diagnosis was made postpartum upon development of fever 3 days postpartum.

1.4 CURRENT RECOMMENDATIONS FOR PERINATAL MONITORING & CARE

To date, the SOGC recommends enhanced pregnancy surveillance for pregnancies in which the mother has developed COVID-19 and continuous external fetal monitoring in labour as there have been higher rates of fetal distress noted in the small case series published to date. The recommendations are built on contemporaneous understanding of the virus and will be modified if new information is available. It is recommended that the infant be tested within approximately 2 hours of birth and assessed for signs of COVID-19 both immediately and through the following 14 days with virtual follow-up after discharge.

The Canadian maternity care system is a global leader and informs maternity care in many countries internationally. With an assembled pan Canadian team, we are poised to provide critical Canadian data to guide healthcare for pregnant women and their infants both nationally and internationally. Evidence-based, SARS-CoV-2 informed recommendations for maternity care are urgently needed. Globally, our team is uniquely situated to acquire and analyze data on SARS-CoV-2 in pregnancy and assess related maternal and infant outcomes. As evidenced in other countries, a time-sensitive, infectious diseases informed response to the pandemic is critical to reduce disease transmission, mortality, and general societal impact. Early initiation of a perinatal SARS-CoV-2 surveillance program will help allow Canada to determine key data and develop evidence-based recommendations for maternity care providers and pregnant women impacted by SARS-CoV-2. Given our other ongoing Canadian perinatal surveillance initiatives, if significant numbers of cases of pregnant women with SARS-CoV-2 are collected, we will also have the ability to do a contemporaneous comparison with pregnant women without infection to determine the likelihood that any complications are related to COVID-19.

2.0 OBJECTIVES

1. By way of contributing BC data, facilitate determination of the burden of SARS-CoV-2 infection in pregnancy in Canada
2. To capture and report maternal outcomes, including degree of respiratory illness and requirement for hospitalization and/or ventilation support
3. To determine fetal and infant outcomes including evidence of transmission of maternal SARS-CoV-2 infection to the infant
4. To provide data to facilitate planning and support for COVID-19 affected pregnancies in the Canadian context

5. To contribute data to international collaborations, allowing for optimized international understanding of COVID-19 in pregnancy

3.0 STUDY DESIGN

3.1 Study Design

This project is a prospective multi-provincial observational surveillance program in Canada to monitor COVID-19 in pregnant women from key referral centres. Data will be collected from care providers of affected pregnancies and will assess pregnancy outcomes and early neonatal outcomes.

Each participating centre will offer consultation and support as needed for cases of COVID-19. The surveillance will be supported by central coordination and data management through the Women's Health Research Institute (WHRI) at BC Women's Hospital and Health Centre, Vancouver.

3.2 Inclusion Criteria

(1) Currently pregnant or recently delivered
(2) Living in Canada
(3) Documented SARS-CoV-2 infection in pregnancy

4.0 PROTOCOL FOR BC SITE

Data collection is approved as a quality improvement/ quality assurance project housed on BC Children's and Women's REDCap platform with the following case identification and data collection approach.

4.1 Case Identification

There are two primary data flow pathways. Patients will initially be identified by a community or hospital-based care provider investigating COVID-19 in a pregnant patient.

Pathway One: Direct referral

Care provider makes a direct referral (to the BC Women's Hospital Reproductive Infectious Diseases Clinic). The Reproductive Infectious Diseases Clinic will engage with the care provider (via phone/secure fax or file transfer) to advise them of COVID-19 in pregnancy surveillance plans and data collection time-points.

Pathway Two: BCCDC notification of case

BCCDC advises the BC surveillance team of positive COVID-19 test results in the context of pregnancy to facilitate provincial surveillance of outcomes. BCCDC provides patient identifiers and care provider name (via the Provincial Health

Services Authority secure file transfer system: IMITS). If this case is already being followed via Pathway One (direct referral pathway), the BC surveillance team will contact the care provider (by phone supplemented by secure fax or file transfer) to inform them of surveillance plans and data collection time points.

4.2 Data Collection

Information (as per data collection forms) will be requested from care provider through phone administered questions or sending of relevant records via secure fax or file transfer to surveillance team for abstraction.

Data collection forms (DCFs) will be completed by the surveillance team and entered into REDCap.

Approved data will be piped into a provincial data access group that feeds into the national REDCap database housed on the BC Children's and Women's REDCap research server. The data access group feature in REDCap is offered for projects that use REDCap from multiple locations/groups. Project Administrators can manage users and rights for data entry occurring at different sites, all within one project. This is done by assigning users to a designated site and to a role. Users designated to a certain site will only be able to create, view and modify data in their designated access group. They will not be able to access or export data from other sites. Data elements to be collected are described in the DCF.

Data collection will include:

1. Dates of potential exposure
2. Reports from testing laboratory for maternal and infant testing, including timing of testing in pregnancy
3. Symptoms of progression of disease
4. Manifestation and severity of disease
5. Pregnancy outcomes: Reports from obstetric care providers, maternal fetal medicine, and/or infectious disease physicians, ultrasound reports, delivery reports, including any specimen results at delivery (i.e., testing for infant)
6. Infant outcomes: at birth and 6-8 weeks of life

Automated systems will be programmed in REDCap to advise sites and coordinators when pending data is expected and when follow up is required to ensure up-to-date, comprehensive surveillance of participants.

4.3 Data Management / Stewardship

Data management will be performed by the coordinating centre, Reproductive Infectious Diseases Team, Women's Health Research Institute, a University of British Columbia Faculty of Medicine Centre at BC Women's Hospital and Health Centre in Vancouver, BC. Completed DCFs will be directly entered via a REDCap

data access group, which allows for siloed entry and access to site-specific data. Regular database maintenance happens bi-monthly at the minimum or when there is a release by the vendor (REDCap Consortium). The data centre (at BC Women's and Children's Hospital) is a physically secured and protected area. The data centre is patrolled by on-site security personnel, monitored by surveillance cameras, and protected by a fire suppression system. Backups of the network are set to run daily and are stored on Backup Servers. The backup retention schedule is currently set at 6 months.

Collected data will be entered into a REDCap database designed to mirror the DCF. Branching will be programmed into data entry to allow for more efficient data entry. Each case will be assigned a unique identification number (ID#). No direct personal identifiers will be included in the national database. Where approved per-site, full infant date of birth will be collected in order to accurately track events occurring within hours or days of birth. Specific birthdates will not be reported. Where approved per-site, maternal or infant date of death, should they occur, will be collected in order to accurately track event timing in relation to disease onset and/or delivery. Specific dates of death will not be reported.

4.4 Statistical Analysis and Metrics

National reporting and analysis will be provided at regular intervals by the coordinating centre to fulfill provincial public health needs, PHAC mandates and align with WHO recommendations. Findings will be reported regularly based on case numbers and novel findings. Summary statistics and project updates will also be posted on our team's University of British Columbia, Reproductive Infectious Diseases Program website.

Data will be summarized using descriptive statistics (e.g. mean and standard deviation or n and percent). Comparisons of maternal/fetal outcomes will be made among different variables (e.g. severity of symptoms, need for ventilation, treatments attempted, maternal age, maternal education, etc.) using generalized linear models with adjustment for confounders where required for the specific outcome. Maternal outcomes will include the risk for preterm birth and delivery complications. Fetal outcomes will include Apgar scores at 1 and 5 minutes, birthweight, admission to NICU, positive test for SARS-CoV-2, and need for resuscitation at delivery.

Missing variables will be excluded or imputed using multiple imputation depending on the scale of missingness, and the needs of the analysis. Statistical analyses will be carried out in the statistical package R v3.5.

Results will be published in peer-reviewed journals and will be presented at national and international conferences, in addition to the regular provincial and national public health reporting.

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