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Severe and critical COVID-19 in pregnancy: A case series from Montreal

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Abstract

Background: Optimal obstetric management for women with coronavirus disease (COVID-19) is not known. We describe the management of six pregnant women requiring in-hospital care for severe COVID-19.

Methods: A retrospective chart review was conducted to identify pregnant women who tested positive for Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) between 15 March and 30 June 2020. A subset of women meeting criteria for severe COVID-19 was included.

Results: Four women required non-invasive supplemental oxygen therapy and two required mechanical ventilation. Four women were discharged from hospital undelivered and two required preterm delivery. One woman had a pulmonary embolism, and two required re-admission for worsening symptoms.

Conclusion: Management of pregnant women with severe COVID-19 is complex and should involve multidisciplinary expertise. Avoiding early delivery may be a safe option. We recommend an individualized approach to care, including careful consideration of the expected risks and benefits of expectant obstetric management versus delivery.

Keywords

COVID-19, coronavirus, critical care, delivery, intensive care unit, mechanical ventilation, pregnancy, supplemental oxygen symptoms, thromboprophylaxis

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Introduction

Pregnant women are more susceptible to severe manifestations from certain viral infections due to pregnancy-related immunological changes.[1] Furthermore, they are at higher risk of hypoxemia due to a decreased functional residual capacity (FRC) and are more likely to develop acute respiratory distress syndrome (ARDS) from physiologically increased capillary leak.[2–4] Accordingly, acute respiratory syndromes from past coronavirus epidemics, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), were associated with maternal mortality rates as high as 10 and 34%, respectively.[5] Whilst Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) disease does not appear to be associated with increased mortality among pregnant women, data from the Centers for Disease Control and Prevention (CDC) revealed that pregnant women may be at higher risk of intensive care unit (ICU) admission and mechanical ventilation than non-pregnant women after adjustment for demographic characteristics and comorbid conditions.[6] The current paper describes the clinical management of six pregnant women treated for severe coronavirus disease (COVID-19) at a tertiary care center in Montreal, Quebec.

Methods

The Jewish General Hospital (JGH) is a tertiary care center in Montreal, Quebec and a teaching site for McGill University. The JGH provides specialized obstetric care, with over 4000 births annually, and comprises a Level III Neonatal Intensive Care Unit (NICU). Quebec, and more specifically Montreal, was the epicenter of the COVID-19 pandemic in Canada during the first wave of infection.[7] The JGH was the first designated COVID-19 hospitalization center for pregnant and non-pregnant adults in Quebec and is therefore uniquely situated to report valuable data on its initial experience treating pregnant women with COVID-19.

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A retrospective chart review was conducted to identify pregnant women who tested positive for SARS-CoV-2 between 15 March 2020 and 30 June 2020. A subset of these women were then included if they required in-hospital antepartum care for COVID-19, with clinical signs of pneumonia and at least one of the following severity criteria defined by the World Health Organization (WHO) for severe COVID-19 pneumonia or critical disease: respiratory rate greater than 30 breaths/min, severe respiratory distress and an oxygen saturation less than 90% on room air (RA), and mechanical ventilation.[8] This study was conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2018) and was approved by the Research Ethics Board of the CIUSSS West-Central Montreal (Project #2021-2346).

Results

From 15 March to 30 June 2020, six out of 41 pregnant women with SARS-CoV-2 were admitted to hospital for inpatient management of COVID-19 and had an oxygen saturation on RA less than 90% or a respiratory rate over 30 breaths/min, thereby meeting criteria for severe COVID-19 pneumonia.[8] All women tested positive for SARS-CoV-2 by polymerase chain reaction test on nasopharyngeal swab and had chest radiographic findings consistent with COVID-19 pneumonia.[8] Of these, two required mechanical ventilation. Table 1 describes the clinical characteristics, management, and outcomes of these women.

Case 1

A 26-year-old woman in her first pregnancy presented to a community hospital's emergency department (ED) at 19 weeks and two days of gestation with cough and fever. SARS-CoV-2 testing was positive, and a chest radiograph showed bilateral airspace opacities compatible with COVID-19 pneumonia. The woman's respiratory status was stable, and she was discharged home on oral amoxicillin-clavulanate 875–125 mg twice daily. One week later, at 20 weeks and two days of gestation, she presented to our hospital's ED with worsening dyspnea, diarrhea, nausea and vomiting. Repeat chest radiograph showed patchy opacities and worsening lower lobe consolidation. In view of her significant respiratory distress, she was admitted to the ICU for close monitoring. On day 2 of admission, the woman had an acute desaturation requiring 15 L/min of supplemental oxygen via non-rebreather mask and worsening work of breathing for which she underwent prompt endotracheal intubation. She was thereafter ventilated as per ARDSNet low positive end-expiratory pressure (PEEP) protocol.[9] Sedation consisted of a combination of infusions of propofol, fentanyl, and midazolam titrated for a target Richmond Agitation-Sedation Scale (RASS) score of –1 to –2. Empirical therapy for bacterial pneumonia included intravenous ceftriaxone 2 g IV daily and azithromycin 500 mg daily. In addition, she was given oral hydroxychloroquine 200 mg three times a day and prophylactic anticoagulation with subcutaneous dalteparin 5000 U daily. At 24-h post-intubation, the PaO_2/FiO_2 ratio was 173. After six days of mechanical ventilation, the woman was successfully extubated to high-flow nasal cannula (HFNC), and the supplemental oxygen was rapidly weaned. An obstetric ultrasound was performed during admission, which revealed no abnormalities. The woman was discharged home on hospital day 11 and resumed her antenatal care at the referring hospital.

Case 2

A 33-year-old woman in her first pregnancy presented with fever and cough at 28 weeks and two days of gestation. SARS-CoV-2 testing was positive. At 29 weeks of gestation, the woman was admitted to the ICU in the context of worsening dyspnea and increased work of breathing. Empiric therapy for bacterial pneumonia included antibiotics (intravenous ceftriaxone 2 g daily and oral azithromycin 500 mg daily), oral hydroxychloroquine 200 mg three times a day, and prophylactic anticoagulation with subcutaneous dalteparin 5000 U daily. On admission, the woman acutely desaturated despite HFNC at 50 L/min and was intubated with an endotracheal tube. She was ventilated with volume-control assist-control (VC/AC) mode of ventilation with an initial PEEP of 16 cm H_2O. Sedation consisted of infusions of propofol, fentanyl, and midazolam titrated for a target RASS score of –1. At 24-h post-intubation, the PaO_2/FiO_2 ratio was 178. Her oxygenation improved rapidly, and she was successfully extubated after 48 h. While intubated, the woman was placed on continuous fetal heart rate monitoring, which revealed an atypical tracing with minimal variability and periods of repetitive variable decelerations. A course of betamethasone was administered for fetal lung maturation in anticipation of a possible preterm delivery. However, the fetal heart rate abnormalities resolved spontaneously as the maternal respiratory status improved. The woman was transiently hypoxic following extubation. This was thought to be multifactorial due to shunting in the setting of COVID-19 and atelectasis post-extubation as well as fluid redistribution with probable non-cardiogenic pulmonary edema. Hypoxia resolved after 24 h of oxygenation with HFNC, mobilization, and administration of furosemide. Following the acute event, she had a normal BNP, and a transthoracic echocardiogram showed a normal ejection fraction with no wall motion abnormality or valvulopathy. The woman was discharged home on hospital day 10 on no additional medication. The woman subsequently presented in labor and had a vaginal delivery at 37 weeks and five days of gestation. Birthweight was 3260 g.

Case 3

A 37-year-old woman in her third pregnancy presented to a community hospital at 31 weeks of gestation with cough and dyspnea. She tested positive for SARS-CoV-2. She was prescribed an outpatient course of oral azithromycin 250 mg daily and was discharged home. Two days later, she presented to our hospital's ED with worsening respiratory symptoms. Chest radiograph on admission revealed bilateral airspace infiltrates, suggestive of COVID-19. The woman had a resting oxygen saturation of 87% on RA and was admitted to the COVID medical ward, where she required supplemental oxygen by nasal cannula at 3 L/min to maintain an oxygen saturation of at least 95%. She was treated empirically with intravenous ceftriaxone 2 g daily and received prophylactic weight-adjusted anticoagulation with subcutaneous dalteparin 7500 U daily. Daily non-stress tests during admission were normal. The woman was weaned to RA on day 7 of admission and discharged home the next day. She subsequently had an uneventful scheduled repeat caesarean section at 39 weeks of gestation. Birthweight was 3970 g.

Case 4

A 31-year-old woman in her second ongoing pregnancy presented to the obstetric triage at 23 weeks and five days of gestation with fever, decreased fetal movement, and mild cough. SARS-CoV-2 testing was positive. Her past medical history was notable for hypothyroidism. The woman was admitted to the Internal Medicine ward and treated empirically with oral azithromycin 250 mg daily and intravenous ceftriaxone 2 g daily for possible bacterial superinfection based on clinical symptoms and the presence of a left lower lobe infiltrate on chest radiograph. She was also given prophylactic anticoagulation with subcutaneous enoxaparin 40 mg daily. Although her saturation was normal on RA, she was admitted for monitoring because of significant work of breathing with a respiratory rate greater than 30

Table 1. Pregnant women with severe and critical COVID-19.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	26	33	37	31	40	35
GA diagnosis (weeks)	19^{+2}	28^{+2}	31^{+1}	23^{+5}	30^{+6}	30^{+4}
GA admission (weeks)	20^{+2}	29^{+0}	31^{+3}	24^{+3}	32^{+0}	31^{+3}
Medical comorbidities	–	Gestational diabetes, requiring insulin	Obesity, type 2 diabetes, requiring insulin	Asthma, hypothyroidism	Asthma, obesity, chronic hypertension	–
Pregnancy risk factors	–	–	–	–	Twin pregnancy	Twin pregnancy
Labs and vitals						
Admission vitals (BP, HR, RR, O_2, Tmax)	104/62, 122, 28, 95% RA, 37.9°C	114/70, 120, 25, 85% RA, 39.0°C	94/64, 95, 32, 92% RA, 36.2°C	120/85, 122, 26, 99% RA, 39.0°C	144/80, 96, 39, 90% RA, 37.0°C	110/64, 100, 22, 92% RA, 36.9°C
Labs on admission						
WBC ($\times 10^9$/L)	5.9	11.2	8.2	10.2	11.3	10.2
Plt ($\times 10^9$/L)	213	351	219	189	238	261
CRP (mg/L)	79.9	111.8	157.3	41.1	115	28.5
PCT (mcg/L)	0.17	0.21	0.44	0.12	0.11	0.22
D-dimer (μg FEU/L)	1553	787	873	1638	1045	1238
Venous blood gas (pH/pCO_2*/bicarbonate #mmol/L)	7.44/29/20	7.44/29/20	7.31/32/19	7.46/32/23	7.38/29/17	7.50/28/22
Disposition	ICU, Medicine	ICU, Medicine	Medicine	Medicine	ICU	Antepartum ward, Medicine
Treatments						
Oxygen therapy	Mechanical ventilation	Mechanical ventilation	Nasal cannula	Nasal cannula	Non-rebreather mask	Nasal cannula
Antibiotics and antivirals	amoxicillin clavulanate 875–125 mg PO BID, followed by ceftriaxone 2 g IV daily and azithromycin 500 mg IV daily	Ceftriaxone 2 g IV daily and azithromycin 500 mg PO daily, followed by Amoxicillin clavulanate 875–125 mg PO BID	Ceftriaxone 2 g IV daily and azithromycin 250 mg PO daily	Ceftriaxone 2 g IV daily and azithromycin 250 mg PO daily, followed by amoxicillin clavulanate 875–125 mg PO BID	Ceftriaxone 2 g IV daily and azithromycin 500 mg IV daily	Azithromycin 250 mg PO daily (post-partum only)
Corticosteroids	–	Betamethasone 12 mg IM × 2 doses	–	–	Betamethasone 12 mg IM × 2 doses	Betamethasone 12 mg IM × 1 dose
Magnesium sulfate	–	–	–	–	–	4 g IV loading dose followed by 1 g/h × 4 h prior to delivery
Other treatments	Hydroxychloroquine 200 mg PO TID	Hydroxychloroquine 200 mg PO TID	–	–	–	–
LMWH	Prophylactic Dalteparin 5000 U SC daily	Prophylactic Dalteparin 5000 U SC daily	Prophylactic Dalteparin 7500 U SC daily	Therapeutic Enoxaparin 105 mg SC daily	Prophylactic Dalteparin 5000 U SC BID	Prophylactic Dalteparin 5000 U SC daily (post-op only)
Outcome						
Obstetric discharge	Antepartum	Antepartum	Antepartum	Antepartum	Post-partum (c/s)	Post-partum (c/s)
Length of stay in hospital (total days)	11	8	8	9 (3 + 6)	14	6 (2+4)

GA: gestational age; BP: blood pressure; HR: heart rate; RR: respiratory rate; O_2: oxygen saturation; RA: room air; T: temperature; WBC: white blood cell count; CRP: C-reactive protein; PCT: procalcitonin; PE: pulmonary embolism; LMWH: low molecular weight heparin; TID: three times daily; SC: subcutaneous; IM: intramuscular; BID: twice daily. *(mmHg)

breaths/min. She clinically improved and was discharged home on day 3 of admission on oral antibiotics (oral amoxicillin and clavulanate 875–125 mg twice daily), without prophylactic anticoagulation post-discharge. However, she returned to hospital two days later with worsening dyspnea and pleuritic chest pain, requiring supplemental oxygen via nasal canula at 2 L/min to maintain an oxygen saturation greater than 95%. In view of her evolving symptomatology, a computed tomography pulmonary angiogram (CTPA) was performed, which revealed the presence of an acute right lower lobe segmental pulmonary embolism. Therapeutic subcutaneous enoxaparin (1.5 mg/kg) daily was initiated, and a transthoracic echocardiogram was performed, revealing a normal ejection fraction and no sign of right ventricular failure or strain. Following clinical improvement, the woman was discharged home on hospital (re-admission) day 6. Subsequently, an induction of labor was planned to manage her anticoagulation. She had an uneventful spontaneous vaginal delivery at 38 weeks and two days of gestation. Birthweight was 3505 g.

Case 5

A 40-year-old woman in her second pregnancy with a monochorionic diamniotic twin pregnancy presented to the ED with productive cough and subjective fever at 30 weeks and six days of gestation. Her past medical history was significant for obesity, chronic hypertension, and reactive airway disease. She was initially tachycardic at 116 beats/min, and her heart rate normalized following administration of intravenous fluids. SARS-CoV-2 testing was positive, and the woman was discharged home with outpatient follow-up. One week later, she returned with worsening dyspnea and new hemoptysis and required 3 L/min of supplemental oxygen via nasal cannula to maintain an oxygen saturation of at least 95%. A chest CTPA ruled out central or segmental pulmonary embolism and revealed extensive bilateral airspace opacities compatible with extensive COVID-19 pneumonia. The woman was admitted to the ICU for observation, where she required up to 4 L/min of supplemental oxygen and was treated empirically for bacterial pneumonia with intravenous azithromycin 500 mg daily and ceftriaxone 2 g daily. Due to the woman's elevated BMI, a higher thromboprophylaxis dose consisting of subcutaneous dalteparin 5000 U twice daily was also administered while in hospital. During admission, the woman developed high blood pressure and was found to have new-onset proteinuria with a urine protein to creatinine ratio of 0.43 g/g (48.6 mg/mmol), thereby meeting the criteria for superimposed preeclampsia. As such, betamethasone was administered in anticipation of a possible preterm delivery. Preterm premature rupture of membranes (PPROM) occurred on the second day of admission. In the context of persistent maternal increased work of breathing, superimposed preeclampsia, and PPROM, an early delivery was recommended. The woman underwent a caesarean section at 32 weeks and three days of gestation for malpresentation of the presenting twin. Magnesium sulfate was not administered due to concerns for respiratory status. Birthweights were 1650 and 1780 g. Post-partum, the woman was successfully weaned off oxygen and transferred to the post-partum wards on post-operative day 1. After improvement in exertional dyspnea, blood pressure, and COVID-19-associated gastrointestinal symptoms, she was discharged home on post-operative day 11 (hospital day 14) on increased doses of antihypertensive agents.

Case 6

A 35-year-old woman in her 11th ongoing pregnancy with a dichorionic twin pregnancy presented to hospital at 30 weeks and four days of gestation with dyspnea, myalgia, nausea, and vomiting. She tested positive for SARS-CoV-2. She was admitted to the antepartum ward and clinically improved following intravenous hydration. She was discharged home undelivered on hospital day 2. Two days later, she was readmitted with increased work of breathing, oxygen saturation under 90% on RA, and threatened preterm labor. One dose of betamethasone was administered. Due to concern of potential respiratory deterioration, an early delivery was recommended. Magnesium sulfate was administered for fetal neuroprotection, and the woman was delivered 4 h later, at 31 weeks, and two days by caesarean section for malpresentation of the presenting twin. Birthweights were 1930 and 1960 g. Post-partum, the woman was transferred to the Internal Medicine ward for observation, where she was treated empirically with oral azithromycin 250 mg daily and subcutaneous dalteparin 5000 U daily for thromboprophylaxis while in hospital. She was gradually weaned off supplemental oxygen therapy and was discharged home on post-operative day 3.

Discussion

Principal findings

In this case series, we describe six pregnant women with severe COVID-19 pneumonia. Of these, two required mechanical ventilation. Three women received betamethasone for fetal lung maturation in the setting of an anticipated preterm delivery before 35 weeks of gestation. While magnesium sulfate was administered to one woman for fetal neuroprotection, it was withheld for eclampsia prophylaxis in another woman. Four women were undelivered at hospital discharge. Importantly, two women had been recently discharged from the ED with mild respiratory concerns prior to admission, and two women required re-admission after hospital discharge.

Clinical implications

Data from the CDC on 8207 pregnant women with SARS-CoV-2 in the United States revealed that pregnant women were at higher risk of requiring admission to the ICU and mechanical ventilation than non-pregnant women of reproductive age.[6] Moreover, the public health agency of Sweden has reported a fourfold increased risk of intubation in pregnant women with COVID-19 as compared to age-matched controls.[10] In our series, the three women who required ICU admission initially presented with mild symptoms, and two of these women were discharged home from the ED after their initial presentation. As such, we recommend close surveillance for all pregnant women with COVID-19 with early consultation with Maternal-Fetal Medicine and ICU specialists, irrespective of symptom severity at presentation. We hereby review several aspects of the management of pregnant women with severe and critical COVID-19, including optimal oxygenation, pharmacological management, and timing of delivery.

Oxygenation and mechanical ventilation of the pregnant woman

Physiologic changes during pregnancy increase the risk of acute respiratory failure and the need for mechanical ventilatory support.[11] While intrinsic lung compliance is unaltered, chest wall and total compliance decrease by approximately 30% in pregnancy.[11–13] The risk of respiratory failure is further increased by the decrease in functional residual capacity (FRC). Mechanical ventilation in pregnant women poses many challenges, including the increased risk of intubation failure due to increased airway edema, decreased FRC, and higher risk of aspiration.[14] Because of reduced chest wall compliance caused by the gravid uterus, increased plateau airway pressures may be noted, and careful attention to these pressures is required. Lung protective ventilation targeting 6 ml/kg of predicted body weight and limiting plateau

pressures below 35 cm H_2O is recommended.[1,2] The gravid uterus will cause increased atelectasis leading to hypoxemia. Therefore, the pregnant woman may require higher levels of PEEP than the non-pregnant woman.[2] Careful attention to maternal carbon dioxide levels is also important, and the usual practice of permissive hypercapnia in severe ARDS should be avoided, as maternal CO_2 retention may lead to fetal acidosis, causing a right shift in the oxygen-hemoglobin dissociation curve and altering the oxygen carrying capacity of fetal hemoglobin.[2,15] Similar to non-pregnant women, other oxygenation strategies in COVID-19 for pregnant women include HFNC, which provides higher delivered oxygen levels and low levels of PEEP, and may reduce the need for mechanical ventilation.[16]

Magnesium sulfate

Magnesium sulfate may lead to an increased risk of respiratory depression.[17] However, it is not associated with an increased risk of respiratory failure.[17] As such, a case-by-case assessment of risks and benefits must be performed, particularly among pregnant women requiring supplemental oxygen who are not mechanically ventilated. Accordingly, several professional societies support the use of magnesium sulfate for pregnant women with COVID-19.[18–20]

Betamethasone

Professional societies currently support the use of corticosteroids when indicated for fetal lung maturation among pregnant women with COVID-19.[18–25] In fact, a 10-day course of dexamethasone for the management of hospitalized women with COVID-19 was associated with a reduction in mortality.[26] However, this information was not available at the time of management of women in this series.

Timing of delivery

Decisions regarding timing and mode of delivery are made on an individual basis, and variability in management is apparent in published case series.[27–30] While alleviating pressure from the gravid uterus may be beneficial for lung mechanics, there is a potential concern for an immune restitution in the early post-partum period which could trigger a clinical deterioration, as has been described with other pathogens.[31] In a case series of five pregnant women requiring endotracheal intubation, Hirshberg et al.[29] report on three women who required preterm delivery for worsening maternal respiratory status and improved following delivery. In contrast, Hantoushzadeh et al.[30] report on seven maternal deaths due to COVID-19, six of which occurred post-partum in the context of worsening clinical status despite delivery. We describe four cases in which conservative obstetric management was chosen, including two women who required mechanical ventilation and were discharged home without requiring emergency delivery. These cases, along with two similar cases described by Hirshberg et al.,[29] suggest that maternal clinical status may improve without delivery. Avoiding iatrogenic preterm delivery and its associated morbidity and mortality is especially important for women who present with severe and critical COVID-19 at earlier gestational ages.

Thromboprophylaxis

Both pregnancy and infection are associated with an increased risk of thrombotic complications, which are an emerging cause of morbidity and mortality related to COVID-19.[32] The mechanism is likely multifactorial, although the interrelationship between inflammation and the coagulation system, or thromboinflammation, appears to play a role.[33] In a retrospective study of 184 women in the ICU with COVID-19, authors reported a cumulative incidence of 31% of a composite outcome of symptomatic pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism.[34] Moreover, an incidence of venous thromboembolism (VTE) of 34% at 14 days of admission was reported in a case series from Europe, with a significantly higher rate of VTE in the ICU population.[35] It remains unclear whether severe COVID-19 confers a higher risk of thrombosis compared to other critical conditions. In our case series, we describe a case of VTE which occurred despite administration of thromboprophylaxis. Guidance statements have recommended thromboprophylaxis for all admitted patients with COVID-19.[35–37] In addition, prophylaxis following discharge in the pregnant population may be considered.[37] Whether a prophylactic dose of anticoagulation is sufficient to prevent thrombotic complications in COVID-19 needs to be determined, and clinical trials are currently underway.[38]

Strengths and limitations

As a dedicated COVID-19 hospitalization center in Canada's epicenter for COVID-19, this study provides valuable insight on the initial experience with treating pregnant women with severe COVID-19. Furthermore, we provide details regarding the obstetric management of these women. Our study was limited by its small sample size, which precluded us from presenting aggregated estimates.

Conclusion

Pregnant women with COVID-19 may be at increased risk of requiring ICU admission and mechanical ventilation. our case series illustrates that women with twin pregnancies or comorbidities may be particularly vulnerable, and that need for supplemental oxygen and inpatient management for COVID-19 do not represent isolated indications for delivery. Until more robust data regarding the management of critically ill pregnant women and their obstetric outcomes become available, studies such as ours may provide valuable guidance to physicians caring for critically ill pregnant women with COVID-19. In these cases, decisions must be made on an individual basis using a collaborative multidisciplinary approach involving obstetric medicine, intensive care, maternal-fetal medicine, and neonatology, which balances maternal risk and benefit of delivery with the burden of prematurity. Furthermore, when possible, pregnant women with severe COVID-19 should be cared for in tertiary care centers with capabilities for fetal health surveillance outside of the obstetric unit.

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Ethical approval

This study was approved by the Research Ethics Board of the CIUSSS West-Central Montreal.

Informed consent

In lieu of individual informed consent of participants, authorization to access patient charts for this retrospective chart review was

obtained from the Director of Professional Services at the Jewish General Hospital.

Guarantor

MJT.

Contributorship

MJT, IM CM and HA conceived the study. MJT was involved in protocol development, gaining ethical approval, and data collection. MJT, CM, CS, JL and IM wrote the first draft of the manuscript. All authors reviewed the manuscript and approved the final version of the manuscript.

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