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Possible formation of pulmonary microthrombi in the early puerperium of pregnant women critically ill with COVID-19: Two case reports

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ABSTRACT

Background: Limited data are available on the management of pregnant women with severe or critical forms of COVID-19, such as the optimal timing of provider-initiated delivery, and post-partum care, including antithrombotic prophylaxis. We present the clinical course, pre- and post-partum management, and outcomes of two pregnant women critically ill with COVID-19.

Cases: Both women had confirmed SARS-CoV-2 pneumonia with rapid clinical decompensation that required admission to the intensive care unit, intubation, and delivery by emergency cesarean section at 32 and 29 weeks. Both patients clinically improved in the first two postoperative days, but this was followed by clinical, laboratory and radiological deterioration on the third postoperative day; however, they both improved again after full anticoagulation. This pattern suggests the possible formation of pulmonary microthrombi in the early puerperium. We discuss the challenges faced by the multiprofessional team in the management of these patients.

Conclusions: There are few resources to guide health professionals caring for pregnant women with critical COVID-19. These two cases contribute to the rapidly evolving knowledge on the management and outcomes of pregnant women with COVID-19.

1. Introduction

Disease severity in pregnant women with COVID-19 is similar to that in non-pregnant adults. Most (86%) will develop a mild form of the disease, while 9.3% will become severely ill (respiratory rate >30 breaths/min, or oxygen saturation ≤ 93% on room air, or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) ⟨< 300), and 4.7% will become critically ill (respiratory failure, septic shock and/or multiple organ failure) [1]. The physiologic changes of pregnancy can bring additional risks to critically ill pregnant patients [2]. Limited data are available on the management of pregnant women with critical COVID-19, such as the optimal timing of delivery, and post-partum care, including antithrombotic prophylaxis.

We describe two cases of pregnant women with critical COVID-19 managed in a single center with possible pulmonary microthrombi after cesarean delivery. The report was approved by the institution's review board; patients gave informed consent.

2. Cases

2.1. Patient 1

An obese (BMI 33 kg/m^2), 44-year-old white nulliparous woman with a singleton pregnancy presented at the hospital's emergency room at 32 weeks of gestation with myalgia and dry cough that had started 15 days earlier (covid day 1), fever in the last 7 days (covid day 7), and dyspnea in the last 24 h (covid day 14). She had a history of breast cancer treated four years earlier with surgery, chemotherapy, and radiotherapy. During chemotherapy, she had had right upper arm thrombosis treated with full-dose enoxaparin for three months and prophylactic enoxaparin for another three months.

Her temperature was 37.5 °C, heart rate (HR) 109/min, blood pressure (BP) 109 × 65 mmHg, respiratory rate (RR) 18/min and O^2 saturation (SpO2) 93% on room air (pulse oximetry). Nasopharyngeal swab for SARS-CoV-2 (RT-PCR) was positive. She was admitted to the intensive care unit (ICU) and received oxygen 2 L/min

Abbreviations: BMI, Body mass index; BP, Blood pressure; CS, Cesarean section; CT, Computed tomography; HR, Heart rate; ICU, Intensive care unit; NICU, Neonatal intensive care unit; PaO2/FiO2, Partial pressure of arterial oxygen /fraction of inspired oxygen; RR, respiratory rate; SpO2, Oxygen saturation.

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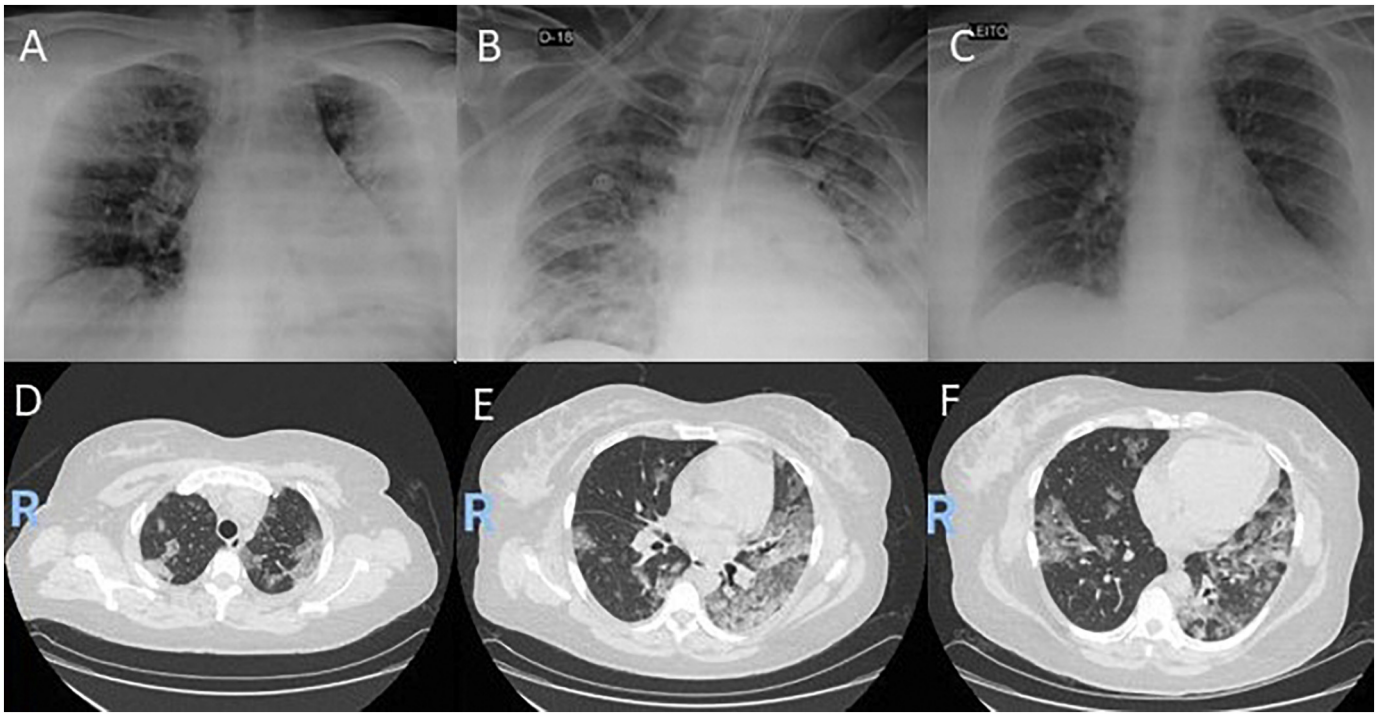

Fig. 1. Imaging findings of patient 1. A, B and C: Anteroposterior chest X-rays. A: 1st hospital day with bilateral, mostly peripheral areas of consolidation. B: 6th hospital day/3rd day post-Cesarean extensive bilateral ground-glass opacities in central and inferior lobes. C: 10th hospital day/3 days after full anticoagulation with almost normal findings. D, E and F: Chest CT scans (Lung window) on 1st hospital day with bilateral multiple ground-glass opacities and areas of interlobular septal thickening. Distribution is mostly peripheral and posterior, and affects more extensively central and inferior lobes. Estimated extent of pulmonary involvement: >50%. R: Right.

through a nasal cannula, with initial improvement in oxygen saturation. She received azithromycin, ceftriaxone, oseltamivir and hydroxychloroquine. Chest X-ray showed faint bilateral patchy opacities (Fig. 1A); chest CT had bilateral ground-glass opacities involving >50% of the lungs (Fig. 1D, E, F). Fetal cardiotocography and Doppler ultrasound were normal.

Over the next 12 h, the respiratory pattern worsened, RR increased to 44/min, PaO2/FIO2 decreased from 246 to 177, and oxygen supplementation was increased to 6 L/min. She was intubated in the ICU under rapid sequence, put on lung protective ventilation, received noradrenaline and continuous sedation with midazolam and fentanyl. Six hours after intubation, norepinephrine was increased to maintain mean arterial pressure at 65 mmHg, but PaO2/FiO2 worsened and the patient was transferred to the operating room for an emergency CS due to cardiovascular instability. The surgery was uneventful with normal blood loss (575 mL).

The 1900 g male newborn (1-min and 5-min Apgar scores 1 and 2, respectively) was intubated and transferred to the NICU; he died 9 h later. Umbilical artery blood pH was 6.8, pCO2 114, pO2 82 and lactate 116. Neonatal nasopharyngeal swab was negative for SARS-CoV-2. Placental histology indicated chronic intervillous hypoxemia without chorioamnionitis.

In the immediate postoperative period (hospital day 4/covid day 18), PaO2/FiO2 improved (338) and the patient remained clinically stable over the next two days, despite worsening lung X-ray (Fig. 1B). On hospital day 7/covid day 21 her clinical condition deteriorated again, PaO2/FiO2 declined (243) and leukocytes, platelets, troponin, D-dimer and ferritin increased (Table 1). The multiprofessional team suspected she was developing pulmonary microthrombi and increased antithrombotic prophylaxis (enoxaparin 60 mg/day) to full anticoagulation dose (120 mg/day). On hospital day 12/covid day 26), laboratory exams and radiological pattern improved (Fig. 1C), she was extubated and PaO2/FiO2 remained stable until discharge (hospital day 15/covid day 29) on full anticoagulation.

2.2. Patient 2

A 29-year-old white obese (BMI 30.6 kg/m^2) woman (G2P1) with a singleton pregnancy presented at the emergency department at 28 weeks of gestation complaining of fever and dyspnea with a positive COVID-19 RT-PCR test 7 days earlier. Dyspnea had started in the last 12 h (hospital day 1/covid day 7).

Her medical and obstetric history were unremarkable. She had taken methyldopa 1 g/day from 13 weeks of gestation due to hypertension. She was afebrile, HR was 96/min, BP 146 × 89 mmHg, SpO2 96% on room air, RR 24/min; chest X-ray showed patchy opacities predominantly in the left lung (Fig. 2A). Chest CT scan showed bilateral, mostly peripheral, ground-glass opacities with multiple areas of parenchymal consolidation involving approximately 25% of each lung (Fig. 2D-F). Cardiotocography and fetal Doppler were normal.

She was admitted to the semi-intensive care unit and given azithromycin, hydroxychloroquine and betamethasone (12 mg/day for 2 days for fetal lung maturation). She received oxygen 2 L/min through a nasal cannula with improvement of oxygen saturation. Within 48 h, the respiratory pattern improved, PaO2/FiO2 increased (from 461 to 580) with 3 L of oxygen supplementation; laboratory exams were stable. On hospital day 3 (covid day 9) clinical condition deteriorated, RR increased (35/min) and PaO2/FIO2 decreased (181).

The multiprofessional team decided to intubate the patient and perform an emergency CS. In the operating room she was intubated under rapid sequence and was immediately put on lung protective ventilation. The CS was uneventful, with normal blood loss (320 mL).

Table 1
Laboratory resuls of Patient 1 during hospitalization.

Date	29/03/20	30/03/20	31/03/20	04/04/20	06/04/20	09/04/20	11/04/20
Hospital day	1	2[a]	3[b]	7[c]	9	12[d]	15[e]
Covid day #	15	16	17	21	23	26	29
Hemoglobin (g/dL)	12.8	11.3	12.0	9.3	9.6	10.0	11.6
Leukocytes (per mm3)	13,300	12,900	13,010	15,880	13,410	14,920	12,010
Neutrophils (per mm3)	10,374	10,578	9627	9232	11,130	11,936	7686
Total Lymphocyte (per mm3)	1596	1161	1952	1846	1475	2238	3483
Platelets (per mm3)	261,000	260,000	322,000	566,000	657,000	691,000	621,000
C-Reactive Protein (mg/dL)	15.5	17.0	16.4	32.7	3.4	1.7	1.0
D-Dimer (mcg/mL)		2.33	4.07	6.12	3.09	5.65	5.03
Lactate Dehydrogenase (IU/L)	407	439	609	525	530	357	280
Urea (mg/dL)	13	13	14	25	39	37	32
Creatinine (mg/dL)	0.4	0.4	0.9	0.7	0.6	0.6	0.5
Creatine phosphokinase (IU/L)		169		193		86	
Troponin (ng/L)		11		60	26	17	
Lactate (mg/dL)		6	9	13	12	14	10
PaO2/FiO2 ratio		80/0.45 = 177	111/0.45 = 246	85/0.35 = 243	106/0.40 = 265	105/0.30 = 350	74/0.21 = 352

[a] Intubation.
[b] Cesarean section.
[c] Introduction of the full anticoagulant therapy.
[d] Extubation.
[e] Hospital discharge.

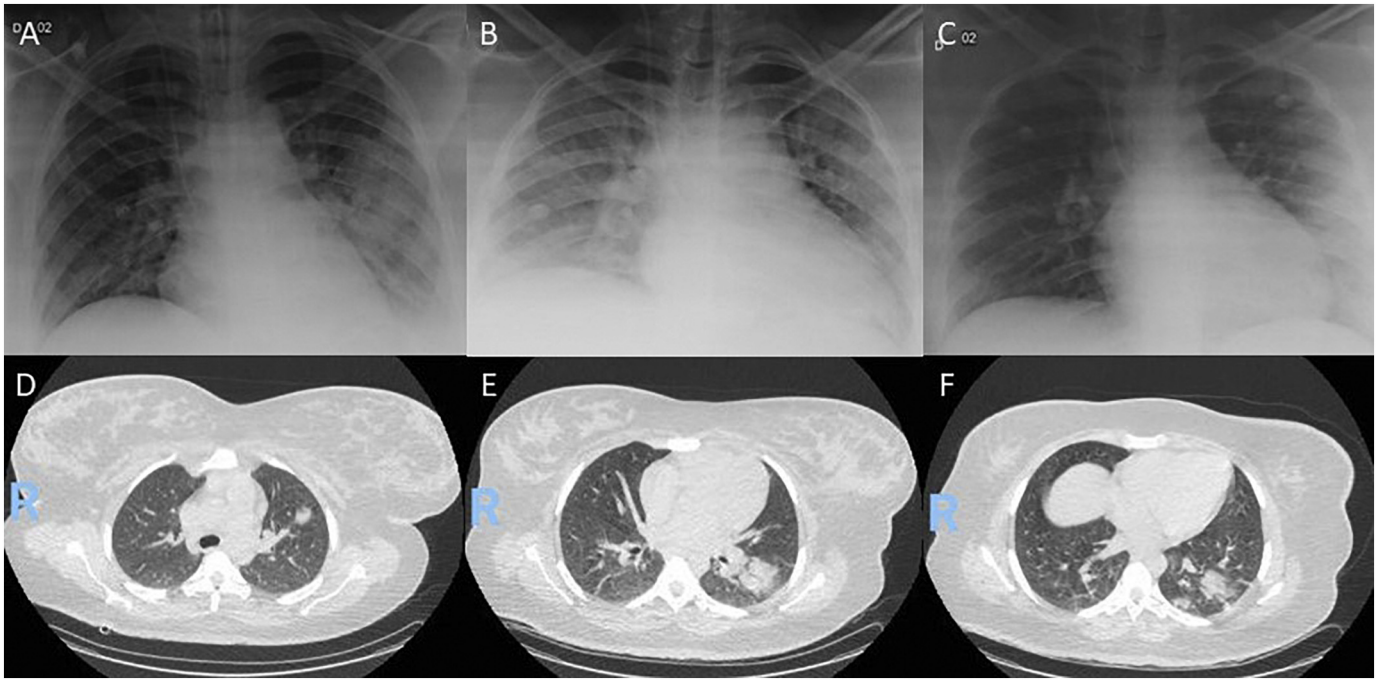

Fig. 2. Imaging findings of patient 2. A, B and C: Anteroposterior chest X-rays. A: 1st hospital day with areas of consolidation in left lung central lobe. B: 6th hospital day/3rd day post-Cesarean, worsening pattern with areas of consolidation in the left lung and mostly peripheral ground-glass opacities in the right lung. C: 11th hospital day/5 days after full anticoagulation, with some areas of consolidation in the left lung, but improved radiological pattern compared to 2.A and B. D, E and F: Chest CT scans (Lung window): 2nd hospital day shows a mixed pattern with bilateral, mostly peripheral and posterior multiple ground-glass opacities associated with areas of consolidation, mostly in the left lung. Estimated extent of pulmonary involvement: <25%. R: Right.

The 1390 g male infant (1-min and 5-min Apgar scores 7 and 9, respectively) was transferred to the NICU; nasopharyngeal swab was negative for SARS-CoV-2 on days 1, 7 and 14.

In the immediate postoperative period, PaO2/FiO2 improved and the patient remained clinically stable (Table 2). On the third postoperative day (hospital day 6/covid day 12) D-dimer increased and chest X-ray images worsened (Fig. 2B). The multiprofessional team suspected that she was developing pulmonary microthrombi and increased prophylactic enoxaparin to a full anticoagulation dose (120 mg/day). She was extubated on hospital day 7/covid day 13 and discharged from the ICU on hospital day 9/covid day 15. On hospital day 11/covid day 17, her clinical condition remained stable, laboratory and radiological exams improved (Fig. 2C), and she was discharged home with enoxaparin anticoagulation.

The neonate remained in hospital (67th day of life, 3545 g) and required O2 during breastfeeding.

3. Discussion

These two cases illustrate the rapid clinical decompensation and management of pregnant patients with COVID-19. Both had an immediate clinical improvement in the first two postoperative days, but this

Table 2
Laboratory results of Patient 2 during hospitalization.

Date	15/04/20	17/04/20	18/04/20	20/04/20	21/04/20	22/04/20	25/04/20
Hospital day	1	3[a]	4	6[b]	7[c]	8	11[d]
Covid day #	7	9	10	12	13	14	17
Hemoglobin (g/dL)	13.2	10.7	10.0	9.1	9.3	9.2	9.4
Leukocytes (per mm3)	8320	5270	7210	9280	9960	10,300	11,350
Neutrophils (per mm3)	6132	4047	5840	7424	6872	7694	7378
Total Lymphocyte (per mm3)	1473	943	1082	1021	2490	1597	2951
Platelets (per mm3)	335,000	290,000	273,000	311,000	360,000	408,000	579,000
B- type Natriuretic Peptide (pg/mL)			9		<5		
C-Reactive Protein (mg/dL)	0.8	0.5	2.8	8.6	10.9	5.6	1.1
Procalcitonin (ng/mL)					0.03		
IL-6 (pg/mL)					25.5	23.8	
D-Dimer (mcg/mL)	0.48	0.45	1.41	2.10	2.62	2.10	2.09
Glutamate Oxaloacetate Transaminase (IU/L)	48	46	48	56	40	35	49
Glutamate Pyruvate Transaminase (IU/L)	56	48	57	50	40	33	68
Ferritin (ng/mL)			92.9		187		
Lactate Dehydrogenase (IU/L)	147	315	220	205	163	195	262
Urea (mg/dL)	10	7	11	20	17	19	22
Creatinine (mg/dL)	0.4	0.3	0.3	0.3	0.4	0.3	0.5
Creatine phosphokinase (IU/L)	20		82	1094	515		
Troponin (ng/L)	<5		7	<5	<5		<5
Lactate (mg/dL)	10	15	<3	4	5	5	7
PaO2/FiO2 ratio	92/0.21 = 461	38/0.21 = 181	193/0.60 = 321	120/0.30 = 400	103/0.35 = 294	71/0.33 = 215	155/0.33 = 470

[a] Intubation and CS.
[b] Introduction of full anticoagulant therapy.
[c] Extubation.
[d] Hospital discharge.

was followed by clinical, laboratory and radiological deterioration on the third postoperative day. Initial improvement after delivery was attributed to reduction of the cardiovascular and pulmonary stress imposed by pregnancy. The subsequent deterioration was attributed to possible microthrombi in pulmonary blood vessels. This hypothesis was based on the coexistence of several prothrombotic conditions (obesity, immobilization, recent surgery, post-partum period) and the finding of increased D-dimer associated with clinical/radiological deterioration. Improvement after full anticoagulation supports this hypothesis.

Thrombotic complications can affect up to 31% of non-pregnant adults in the ICU with SARS-COV-2 pneumonia [3]. Fibrinous thrombi in small pulmonary arterioles in areas of damaged and preserved lung parenchyma, and widespread thrombosis with microangiopathy have been reported in autopsies of COVID-19 patients [4,5].

A CS can potentially increase maternal risks because, in theory, any surgery can increase the inflammatory response induced by COVID-19, exacerbate endothelial dysfunction, and increase the risks of pulmonary and myocardial edema, and cardiac dysfunction [6]. On the other hand, delivery can alleviate maternal cardiac and pulmonary overload and reduce the oxygen consumption imposed by pregnancy [7]. Preterm delivery can lead to neonatal death or long-term disabilities, but the decision to wait until the fetus is more mature can result in an emergency CS due to worsening maternal conditions, exposing the fetus to prolonged maternal hypoxia and the effects of drugs needed for maternal mechanical ventilation. The adverse neonatal outcome in the first case reported above led the multiprofessional team to opt for intubation and immediate CS in the second case, at a much earlier gestational age. The suspicion of pulmonary thrombi after CS in these two cases has led the team to customize post-partum antithrombotic medication in women with severe COVID-19 and other risk factors for thrombosis.

Experience in the management of critical COVID-19 in pregnancy is limited. The largest cohort to date collected data from 12 American hospitals and reported a total of 20 pregnant women with critical COVID-19, 3 of whom were undelivered at the time of publication [8]. All critical cases except one were delivered by CS, at an average gestational age of 32 weeks, mainly due to worsening maternal status. The authors provide no details of the post-partum course of these 17 delivered women, 11 of whom were still hospitalized at the time of publication. [8] There are few resources to guide health professionals caring for pregnant women with critical COVID-19. At present, multiprofessional teams have to make decisions on the optimal management of these cases based their own, albeit limited, experience and on the individual characteristics of each patient.

This is the first publication on critical COVID-19 pregnancies in Brazil. A study limitation is the lack of other coagulation tests (fibrinogen, prothrombin time and activated partial thromboplastin time).

Two critical COVID-19 preterm pregnant patients improved in the first two days after emergency CS, deteriorated on the third post-partum day, and improved again after full anticoagulation. This pattern suggests the possible formation of pulmonary microthrombi in the early puerperium. These two case reports contribute to the rapidly evolving knowledge on the management and outcomes of pregnant women with critical COVID-19.

Contributors

Celso T. Tutiya was responsible for data acquisition, contributed to drafting of the article and approved the final version.

Monica M. Siaulys conceived the study, contributed to data acquisition, drafted the manuscript and approved the final version.

Mario M. Kondo contributed to data analysis and interpretation, revised the manuscript and approved the final version.

Lisia Miglioli contributed to data acquisition and analysis, revised the manuscript and approved the final version.

Elaine Galvão contributed to data acquisition and analysis, revised the manuscript and approved the final version.

Cilene C. Pinheiro contributed to data acquisition and analysis, revised the manuscript and approved the final version.

Maria Regina Torloni contributed to data analysis and interpretation, drafted the article and approved the final version.

Filomena Mello contributed to data analysis and interpretation, revised the manuscript and approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

Obtained.

Provenance and peer review

This case report was peer reviewed.

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