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INTRODUCTION

The present COVID-19 pandemic due to SARS-CoV-2 novel coronavirus has resulted in high numbers of critically ill patients and deaths. Emerging data on the maternal impact of COVID-19 suggest that the clinical course is similar irrespective of pregnancy. However, despite these data, our report of two pregnancies with COVID-19-related, rapidly progressive coagulopathy may warrant caution.

METHODS

2.1 Case 1 (C1)

Forty-year-old gravida 2 para 1, followed at Mount Sinai Hospital, Toronto, Canada, with familial neutropenia diagnosed in infancy,
with an uncomplicated course in adulthood. Pregnancy was complicated by gestational diabetes, neutropenia (0.1-0.3 × 10^9/L), and mild respiratory infections treated with antibiotics. She was commenced on granulocyte colony-stimulating factor (G-CSF) 4 weeks prior to admission and admitted at 35 + 3 weeks' gestation with cough and pyrexia. Normotensive, tachycardic (110-121 beats/min), febrile (39°C), with normal oxygen saturation in room air. Fetal heart rate monitoring was unremarkable. Normal obstetrical ultrasound demonstrated a well-grown fetus. Piperacillin/tazobactam was commenced for febrile neutropenia, and filgrastim was 300 mcg continued (Table 1). SARS-CoV-2 was confirmed by polymerase chain reaction (PCR) on a nasopharyngeal swab. The chest x-ray was normal. Over 48 hours, there was progressive thrombocytopenia, declining fibrinogen, and rising activated partial thromboplastin time (APTT) with concomitant improvement in neutrophil count, responding to G-CSF (Table 1). Respiratory parameters were stable. There was collaboration of obstetric, haematologic, infectious disease, and anesthesiologic teams in her care. Differential diagnoses included COVID-19; sepsis with familial neutropenia masking superimposed bacterial infection; and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. The latter in the absence of hypertension, hemolysis, or proteinuria, was considered extremely unlikely. Mild transaminitis was ascribed to underlying infection (Table 1). Owing to concerns that progressive coagulopathy would preclude neuraxial anesthesia, and aiming to avoid general anesthesia (GA), she was delivered via repeat Cesarean section (CS) under spinal anesthesia on admission day 2. She sustained a postpartum hemorrhage (PPH) of 1.5 L controlled with uterine artery ligation and B-Lynch compression, alongside uuterotonics and blood products (tranexamic acid 2 g, fibrinogen 4 g, cryoprecipitate 10 units). LMWH prophylaxis was initiated 12 hours later. Coagulopathy improvement was noted on postoperative day (POD) 2 (Table 1). Piperacillin/tazobactam was continued. Filgrastim was increased to 480 mcg daily and discontinued on POD3. A healthy male infant was delivered, weighing 2.93 kg (Apgars of 9 and 9 at 1 and 5 minutes). Breastfeeding was initiated with pediatric clearance. Mother and infant were discharged on POD4, with self-isolation instructions.

### 2.2 | Case 2 (C2)

Twenty-three-year-old gravida 1 para 0 admitted to a peripheral hospital at 35 + 2 weeks' gestation with cough and pyrexia (38.6°C). Nasopharyngeal swab demonstrated SARS-CoV-2. Thrombocytopenia, prolonged APTT, and transaminitis (Table 1) triggered transfer to Antoine Béclère Hospital in Clamart, France. Medical history was remarkable for asthma and body mass index (BMI) 32. No evidence of hypertension/proteinuria. Following transfer, there was progressive deterioration in coagulation parameters (Table 1). A non-reassuring fetal heart rate coupled with progressive coagulopathy and transaminitis prompted emergency CS under GA. Fibrinogen 3 g and tranexamic acid 1 g were administered prior to delivery. A male infant was born at 35 + 5 weeks, weighing 2.54 kg (Apgars of 4, 2, 7 at 1, 5, and 10 minutes, respectively). There was no excessive bleeding and coagulopathy resolved by POD1. Prophylactic low molecular weight heparin (LMWH) administered on POD1. Respiratory symptoms remained stable, and she was discharged on POD5.

### 3 | DISCUSSION

This is the first report describing COVID-19-related acutely progressive coagulopathy in the third trimester of pregnancy, the recovery of which appears to be hastened by delivery. Coagulopathy results from concurrent activation of the coagulation and fibrinolytic cascades, here likely triggered by sepsis, causing clotting factor consumption. Manifestations can be either thrombotic or hemorrhagic. Pregnancy adds further complexity, given its physiologically hypercoagulable state, with rising coagulation factors, including a fibrinogen and D-dimers increase to 50% above baseline by the third trimester.

While C1 had underlying familial neutropenia, and plausibly her relatively immunocompromised state contributed to the COVID-19 course, chronic neutropenia is not a recognized cause of pregnancy-associated coagulopathy. A retrospective cohort study examining 38 pregnancies with chronic neutropenia syndromes noted no coagulopathy cases.

Significantly elevated D-dimers were observed in both cases (17-fold upper normal range in pregnancy [UNLP] and 12-fold UNLP). Concerningly, recent reports position elevated D-dimers as a poor prognostic indicator in non-pregnant individuals. Huang et al noted higher D-dimers in those requiring ICU admission versus those who did not (median D-dimer 2.4 mg/L [0.6-14.4] versus 0.5 mg/L [0.3-0.8]; P = .0042). Tang et al observed higher D-dimers in non-survivors versus survivors (2.12 µg/mL [range 0.8-5.3 µg/mL]) versus 0.6 µg/mL [0.4-1.3 µg/mL]). Given the typical D-dimer rise during gestation, it remains unclear what D-dimer threshold would indicate unfavorable prognosis in pregnancy. The International Society on Thrombosis and Haemostasis (ISTH) suggests that those with significant D-dimer elevation (arbitrarily defined as 3- to 4-fold above upper normal limit [UNL]) be hospitalized even in the absence of other concerning symptoms.

Outside of pregnancy, anticoagulation of coagulopathic, septic patients improves outcomes. ISTH established a scoring system to identify “sepsis-induced coagulopathy” (SIC), with a SIC score > 4 indicative of early phase disseminated intravascular coagulation (DIC). Tang et al demonstrated lower 28-day mortality with SIC...
### Table 1: Investigations and Results Timeline

| Laboratory Parameters          | Normal Range   | Case# | Baseline | 2 days Pre-op | 1 day Pre-op | Delivery day | POD1 | POD2 | POD3 |
|-------------------------------|----------------|-------|----------|---------------|--------------|--------------|------|------|------|
| **Blood**                     |                |       |          |               |              |              |      |      |      |
| Hemoglobin (g/L)              | 110-150        | C1    | 130      | 123           | 113          | 123          | 110  | 95   | 93   |
|                               |                | C2    | 130      | 127           | 120          | 96           | 88   | 84   |      |
| White cell count (×10^9/L)    | 3.0-10.0       | C1    | 3.03     | 0.51          | 1.06         | 2.29         | 3.87 | 6.32 | 12.42|
|                               |                | C2    | 8.65     | 4.56          | 2.17         | 4.86         | 5.84 | 4.58 |      |
| Neutrophil count (×10^9/L)    | 1.5-7.0        | C1    | 0.33     | 0.07          | 0.33         | 0.61         | 1.15 | 4.44 | 6.65 |
|                               |                | C2    | 4.01     | 1.50          |              |              |      |      | 4.44 |
| Lymphocyte count (×10^9/L)    | 1.0-3.5        | C1    | 1.52     | 0.16          | 0.40         | 0.77         | 0.85 | 2.31 | 3.42 |
|                               |                | C2    |          | 0.32         | 0.54         |              |      |      | 1.02 |
| Platelet count (×10^9/L)      | 140-400        | C1    | 167      | 127           | 98           | 82           | 78   | 86   | 81   |
|                               |                | C2    | 242      | 118           | 63           | 54           | 71   | 89   | 114  |
| INR                           | 0.9-1.1        | C1    | 1.0      | 1.0           | 1.0          | 1.0          | 1.0  | 1.0  | 0.9  |
|                               |                | C2    |          | 1.0          | 1.1          | 0.9          | 0.9  | 0.9  |      |
| APTT (seconds)                | 18.5-29.9      | C1    | 30.3     | 41.0          | 41.2         | 32.3         | 29.6 |      |      |
|                               |                | C2    | 51       | 60           | 38           | 38            | 37   |      |      |
| Fibrinogen (g/L)              | 1.5-4.2        | C1    | 4.9      | 2.2           | 2.4          | 2.6          | 3.5  |      |      |
|                               |                | C2    | 3.5      | 0.8          | 1.4          |              |      |      |      |
| D-dimer (mg/L)                | 0.13-1.7 (3rd trimester) | C1 | 2.06 | 25.79 | 28.79 | 20.3 | 3.99 |
|                               |                | C2    |          | >20          |              |              |      |      | 1.12 |
| Bilirubin (total) (µmol/L)    | 3.0-20.0       | C1    |          | 6            | 4            | 3            |      |      |      |
|                               |                | C2    |          | 6            | 10           | 7            | 4    | 4    |      |
| Creatinine (µmol/L)           | 45-80          | C1    | 51       | 68           | 70           | 76           | 67   | 72   | 68   |
|                               |                | C2    |          | 39           | 51           | 46           | 56   |      |      |
| AST (unit/L)                  | 13-37          | C1    | 20       | 52           | 67           | 85           | 83   |      |      |
|                               |                | C2    | 33       | 75           | 81           | 112          | 55   | 55   | 32   |
| ALT (unit/L)                  | 10-40          | C1    | 12       | 20           | 20           | 33           | 34   |      |      |
|                               |                | C2    | 37       | 47           | 41           | 100          | 76   | 51   |      |
| Lactic acid (mmol/L)          | 0.5-2.0        | C1    |          | 2.1          |              |              |      |      |      |
|                               |                | C2    |          |              |              |              |      |      |      |
| LDH (unit/L)                  | 135-225        | C1    |          |              |              | 494          |      |      |      |
|                               |                | C2    |          |              |              | 386          | 304  | 246  |      |
| Uric acid umol/L              | 180-360        | C1    |          |              |              | 187          |      |      |      |
|                               |                | C2    |          |              |              |              |      |      |      |
| Creatinine kinase (unit/L)    | 0.0-190        | C1    |          |              |              | 404          |      |      |      |
|                               |                | C2    |          |              |              | 302          |      |      |      |
| C-reactive protein (mg/L)     | <10.0          | C1    |          |              |              | 44.7         |      |      |      |
|                               |                | C2    |          | 92           | 37           | 51           | 139  | 123  |      |
| Ferritin (µg/L)               | 7-191          | C1    |          |              |              | 209          |      |      |      |
|                               |                | C2    |          |              |              | 384          |      |      |      |
| Blood culture                 |                | C1    |          | -ve          |              |              |      |      |      |
|                               |                | C2    |          |              |              |              |      |      |      |
| **Urine**                     |                |       |          |               |              |              |      |      |      |

(Continues)
score > 4 (40% versus 64%; \( P = .029 \)) and D-dimer > 6-fold UNL (33% versus 52%; \( P = .017 \)) in those with versus without anticoagulation. While SIC score use remains unvalidated in pregnancy, given the poor prognostic implication of high D-dimers and benefit of anticoagulation prophylaxis in non-pregnant individuals with COVID-19, consideration of prophylactic LMWH may be valuable in the immediate postpartum period. While Huang et al did not observe significant APTT elevations with COVID-19 outside pregnancy,7 Tang et al noted increased mortality with high APTT, prothrombin time, D-dimer, and fibrin degradation products compared to COVID-19 survivors.8 Neither APTT nor low fibrinogen was assessed in a pregnancy series,11 although both are part of DIC classification.10

Two guidelines addressing coagulopathy in COVID-199,12 highlight D-dimer elevation, thrombocytopenia, and low fibrinogen as poor prognostic indicators of mortality risk. In pregnancy, low fibrinogen was the only coagulation parameter associated with PPH severity; with a positive predictive value of 100% with fibrinogen < 2 g/L.13 C1 demonstrated a rapid deterioration of fibrinogen (4.9-2.2 g/L) and sustained a severe PPH of 1.5 L. While C2 did not experience excessive bleeding, the sharp drop in fibrinogen to 0.8 g/L was treated pre-operatively.

Lymphocytes have a critical role in the immune response to viral infections, with lymphopenia correlating with illness severity and hospitalization in COVID-19.14 In a series from Wuhan, China, including 52 critically ill patients, lymphopenia occurred in 80%.15 Both C1 and C2 had lymphocyte count nadirs of 0.16 and 0.32, respectively. Both also displayed transaminitis (Table 1). Previous experience with SARS and MERS-CoV revealed transaminitis in 60% of cases.16 With COVID-19, at least seven large scale case series showed the presence of transaminitis in 14%-53% of cases during disease progression.16

We highlight a possible link between third-trimester maternal COVID-19 infection and rapid maternal deterioration, with progressive coagulopathy, improving shortly after delivery. To date, no maternal mortality in COVID-19 has been reported; however, as pregnancy may not protect COVID-19 patients from coagulopathy, and coagulopathy is linked to poorer prognosis outside of pregnancy, it may presage impending compromise. The described laboratory derangements can be reminiscent of HELLP syndrome, and thus knowledge of the COVID-19 relationship is paramount for appropriate diagnosis and treatment. As per ISTH recommendations, routine measurements of D-dimers, prothrombin time, and platelet count in all patients presenting with COVID-19 may aid risk stratification. In pregnancy, the measurement of APTT and fibrinogen levels may also be valuable.

**CONFLICTS OF INTEREST**
There are no conflicts of interest.

**AUTHOR CONTRIBUTIONS**
Dr Koumoutsea and Dr Malinowski wrote the first draft and this was edited by all authors.

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