# Disseminated intravascular coagulation complicating mild or asymptomatic maternal COVID-19

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**BACKGROUND:** Hypercoagulability frequently complicates moderate or severe COVID-19 and can result in venous thromboembolism, arterial thrombosis, or microvascular thrombosis. Disseminated intravascular coagulation, however, is uncommon.

**OBJECTIVE:** We sought to describe the clinical presentation and outcome in a series of pregnant patients with mild or asymptomatic COVID-19 who had disseminated intravascular coagulation.

**STUDY DESIGN:** This was a retrospective case series. Cases were solicited via e-mails targeted to obstetrical providers in the Mednax National Medical Group and a restricted maternal–fetal medicine Facebook page. Inclusion criteria were: hospital admission during pregnancy, positive test for SARS-CoV-2 within 2 weeks of admission, and maternal disseminated intravascular coagulation defined as ≥2 of the following: platelet count ≤100,000 per $mm^3$, fibrinogen ≤200 mg/dL, and prothrombin time ≥3 seconds above the upper normal limit. Exclusion criteria were severe COVID-19 requiring ventilation within an hour of diagnosis of coagulopathy or use of anticoagulants at the time of diagnosis. Maternal and newborn records were abstracted and summarized with descriptive statistics.

**RESULTS:** Inclusion criteria were met in 19 cases from October 2020 through December 2021. Of these, 18 had not received any COVID-19 vaccine, and 1 had unknown vaccination status. Median gestational age on hospital admission was 30 weeks (interquartile range, 29–34 weeks). The main presenting symptom or sign was decreased fetal movement (56%) or nonreassuring fetal heart rate pattern (16%). COVID-19 was asymptomatic in 79% of cases. Two of the 3 defining coagulation abnormalities were found in 89% of cases and all 3 in the remaining 11%. Aspartate aminotransferase was elevated in all cases and ≥2 times the upper normal limit in 69%. Only 2 cases (11%) had signs of preeclampsia other than thrombocytopenia or transaminase elevation. Delivery was performed on the day of admission in 74% and on the next day in the remaining 26%, most often by cesarean delivery (68%) under general anesthesia (62%) because of nonreassuring fetal heart rate pattern (63%). Postpartum hemorrhage occurred in 47% of cases. Blood product transfusions were given in 95% of cases, including cryoprecipitate (89% of cases), fresh/frozen plasma (79%), platelets (68%), and red cells (63%). Placental histopathology was abnormal in 82%, with common findings being histiocytic intervillositis, perivillous fibrin deposition, and infarcts or necrosis. Among the 18 singleton pregnancies and 1 twin pregnancy, there were 13 live newborns (65%) and 7 stillbirths (35%). Among liveborn neonates, 5-minute Apgar score was ≤5 in 54%, and among cases with umbilical cord blood gases, pH ≤7.1 was found in 78% and base deficit ≥10 mEq/L in 75%. Positive COVID-19 tests were found in 62% of liveborn infants.

**CONCLUSION:** Clinicians should be alert to the possibility of disseminated intravascular coagulation when a COVID-19 patient complains of decreased fetal movement in the early third trimester. If time allows, we recommend evaluation of coagulation studies and ordering of blood products for massive transfusion protocols before cesarean delivery if fetal tracing is nonreassuring.

**Key words:** decreased fetal movement, intrauterine fetal demise, massive transfusion, placental fibrinoid deposition, placental histiocytic intervillositis, placental necrosis, SARS-CoV-2 placentitis, stillbirth

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## AJOG Global Reports at a Glance

### Why was this study conducted?

Through discussions on a private clinical forum and social media, we discovered that we had found similar cases across the country of pregnant patients with asymptomatic or mild COVID-19 who had disseminated intravascular coagulation (DIC) and who shared other similarities. We sought to collect and describe relevant cases.

### Key findings

Patients typically presented in the early third trimester with decreased fetal movement and/or nonreassuring fetal heart rate pattern. Most were asymptomatic, and all were unvaccinated.

We found high rates of postpartum hemorrhage and multiunit blood product transfusion, fetal compromise including metabolic acidosis and stillbirth, and neonatal SARS-CoV-2 positivity. Placental histopathology suggested viral infection.

### What does this add to what is known?

Severe DIC can occur even if maternal COVID-19 infection appears mild.

## Introduction

COVID-19-associated coagulopathy is a prothrombotic condition that frequently complicates severe COVID-19,[1−11] resulting in venous thromboembolism, arterial thrombosis (eg, acute coronary syndrome or stroke), microvascular thrombosis, or death.[12−14] Because of these complications, the US Centers for Disease Control and Prevention (CDC) recommends prophylactic anticoagulation for patients hospitalized with COVID-19, including pregnant patients.[15,16]

Less commonly, severe COVID-19 triggers disseminated intravascular coagulation (DIC), a consumptive coagulopathy characterized by thrombocytopenia, decreased fibrinogen, prolonged clotting times, and elevated D-dimers.[2,3] DIC carries increased risks of hemorrhage or death.[17]

The incidence of DIC in COVID-19 during pregnancy was 0.7% to 1.3% in 2 large studies,[18,19] but other large studies did not report coagulopathy or DIC as outcomes.[20−22] The large studies provide scant clinical information about the presentation or outcomes of DIC complicating COVID-19 during pregnancy, but case reports have provided key clinical details. Many cases had abnormal fetal heart rate tracings or intrauterine fetal death.[23−28] In reports that included placental histopathology, a pattern of "SARS-CoV-2 placentitis" has been described, a triad of histiocytic intervillositis, perivillous fibrin deposition, and villous trophoblastic necrosis.[24−30]

In mid-October 2021, a maternal−fetal medicine physician (MFM) posted a confidential query on the Perinatology Forum, a protected e-mail-based chat group open to all MFMs employed by the Mednax National Medical Group (Sunrise, FL, recently renamed Pediatrix). The query concerned a patient with recent diagnosis of COVID-19, symptomatic only for a mild cough. Laboratory results included a platelet count of 36,000 per $mm^3$, fibrinogen <50 mg/dL, and prothrombin time of 26.6 seconds (international normalized ratio, 2.1). There was no evidence of placental abruption, sepsis, or other explanation for DIC. The query asked whether anyone had seen similar cases. Within days, 12 MFMs responded that they had managed similar cases of DIC in pregnancies with mild or asymptomatic COVID-19.

Because previous studies have found that adverse pregnancy outcomes with COVID-19 are largely in those with severe or critical disease,[21,31] these cases of DIC with otherwise mild maternal disease seemed noteworthy. Therefore, our objective was to gather as many cases as practical of DIC complicating COVID-19 in pregnancy and to summarize their clinical features.

## Materials and Methods

This was a retrospective, descriptive study based on review of maternal and neonatal hospital records. After the initial case-finding described above, we formalized the protocol and obtained an exempt-status determination from the Western Copernicus Group Institutional Review Board. We then sought additional cases via "blast" e-mails to all MFM and obstetrical hospitalist physicians employed by Mednax. We also solicited cases through posts on the "Society for Maternal-Fetal Medicine Members" Facebook page.

Inclusion criteria were hospital admission from February 2020 through December 2021, pregnancy at any gestational age, positive SARS-CoV-2 test during hospitalization or within the previous 2 weeks, and maternal DIC defined as ≥2 of the following: platelet count ≤100,000 per $mm^3$, fibrinogen ≤200 mg/L, and prothrombin time prolonged ≥3 seconds above the upper limit of normal (pregnancy-specific criteria modified from Clark et al[32] and Erez et al[33]). Exclusion criteria were: severe COVID-19 infection, defined as ventilator support or extracorporeal membrane oxygenation (ECMO) at the time of diagnosis or within 1 hour after diagnosis of DIC; or treatment with anticoagulants at the time of diagnosis of DIC.

For each patient, a case report form with deidentified maternal and newborn data was completed by a treating physician and sent to a central coordinator. Data were entered into a password-protected spreadsheet, exported to a database, and analyzed using Stata, version 13.1 statistical software (StataCorp, College Station, TX). Analyses included descriptive statistics (percentages for categorical variables, median with interquartile range [IQR] for numeric variables). Chi-square or Mann−Whitney *U* tests were used for between-group comparisons, with *P* values <.05 considered significant.

## Results

Case report forms were submitted by 21 physicians for 27 cases. Inclusion criteria were met in 19 cases. We excluded 8

cases that did not meet our definition of DIC. No cases were excluded because of anticoagulant use, ventilator requirement, or ECMO.

Admission characteristics are summarized in Table 1. Gestational age at presentation ranged from 24 to 36 weeks; there were no cases before viability or at term. COVID-19 was diagnosed a median of 5 days before admission (IQR, 3–8 days). In 3 cases, SARS-CoV-2 was detected on routine screening on hospitalization for other indications (abnormal fetal surveillance in 2, preterm contractions in 1). COVID-19 vaccination status was documented for 18 patients; none had received any COVID-19 vaccination. The most common presenting complaint was decreased fetal movement (11 cases, 56%); 3 additional cases were sent to hospital to follow-up nonreassuring fetal heart rate monitoring in outpatient clinics. Most patients were asymptomatic for respiratory or systemic symptoms of COVID-19 infection on admission. Admitting maternal vital signs were normal in all cases except in 1 patient with a temperature of 38.1°C and 1 with a respiratory rate of 34 breaths per minute. In 5 cases, fetal death was diagnosed at admission. Admission laboratory studies were remarkable for platelet count <100,000 per $mm^3$ in all but 1 case, hypofibrinogenemia in 80%, and prolonged prothrombin time in 29%. The aspartate aminotransferase (AST) level was above the upper limit of normal in all cases and was more than twice the upper limit in 69%. In contrast, alanine aminotransferase (ALT) was normal in 75% of cases.

Pregnancy outcomes and maternal course are summarized in Table 2. All cases were delivered on the day of admission (74%) or the next day (26%), most commonly because of nonreassuring fetal heart rate patterns (63%) or fetal death (32%), and most commonly by cesarean delivery (68%). Postpartum hemorrhage was common (47%) and often treated with uterotonic medications such as methylergonovine, carboprost, or misoprostol; 2 cases had peripartum hysterectomy. Blood

**TABLE 1**
**Characteristics on admission**

| Characteristic | Number of observations | Result |
|---|---|---|
| Maternal age, y, median (IQR) | 19 | 31 (27–35) |
| Gravidity, median (IQR) | 18 | 2.5 (1–4) |
| Parity, median (IQR) | 19 | 1 (0–2) |
| Nulliparous, n (%) | 19 | 6 (32%) |
| Previous preterm birth, if parous, n (%) | 13 | 4 (31%) |
| Race/ethnicity | 19 | |
| Non-Hispanic White, n (%) | | 16 (84%) |
| Hispanic, n (%) | | 1 (5%) |
| Not reported, n (%) | | 2 (11%) |
| Gestational age, wk | | |
| Onset of symptoms, median (IQR) | 18 | 28.5 (27–33) |
| Diagnosis of COVID-19, median (IQR) | 19 | 29 (28–33) |
| Admission to hospital, median (IQR) | 19 | 30 (29–34) |
| COVID-19 diagnosis | | |
| Symptom onset, days before admission, median (IQR) | 18 | 9 (4–14) |
| Positive SARS-CoV-2 test, days before admission, median (IQR) | 19 | 5 (3–8) |
| Type of SARS-CoV-2 test | 19 | |
| Polymerase chain reaction | | 11 (58%) |
| Antigen | | 2 (11%) |
| Not reported | | 6 (32%) |
| Year and quarter of admission | 19 | |
| 2020 Q1–Q3, n (%) | | 0 |
| 2020 Q4, n (%) | | 3 (16%) |
| 2021 Q2, n (%) | | 2 (11%) |
| 2021 Q3, n (%) | | 5 (25%) |
| 2021 Q4, n (%) | | 9 (46%) |
| Previous COVID-19 vaccination, n (%) | 18 | 0 |
| Presenting sign or symptom (chief complaint) | 19 | |
| Decreased fetal movement, n (%) | | 11 (56%) |
| Abnormal fetal heart rate tracing, n (%) | | 3 (16%) |
| Preterm contractions, n (%) | | 2 (11%) |
| Bleeding, n (%) | | 1 (5%) |
| Other, n (%) | | 2 (11%) |
| Other presenting symptoms | | |
| Respiratory | | |
| Cough, n (%) | 19 | 1 (5%) |
| Rhinorrhea, n (%) | 19 | 1 (5%) |

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*(continued)*

**TABLE 1**
**Characteristics on admission** *(continued)*

| Characteristic | Number of observations | Result |
|---|---|---|
| Anosmia, n (%) | 19 | 1 (5%) |
| Sore throat, n (%) | 19 | 0 |
| Dyspnea, n (%) | 19 | 1 (5%) |
| No respiratory symptoms | 19 | 16 (84%) |
| Systemic | | |
| Fever (reported), n (%) | 19 | 3 (16%) |
| Chills, n (%) | 19 | 1 (5%) |
| Fatigue, n (%) | 19 | 1 (5%) |
| Headache, n (%) | 19 | 0 |
| Myalgia, n (%) | 19 | 2 (11%) |
| Nausea/vomiting, n (%) | 19 | 0 |
| Abdominal pain, n (%) | 19 | 0 |
| No systemic symptoms | 19 | 16 (84%) |
| No respiratory or systemic symptoms | 19 | 15 (79%) |
| Comorbidities | | |
| Obesity, n (%) | 19 | 3 (16%) |
| Diabetes mellitus | | |
| Gestational diabetes mellitus, n (%) | 19 | 1 (5%) |
| Other diabetes mellitus, n (%) | 19 | 0 |
| Hypertensive disorder | | |
| Preeclampsia, n (%) | 19 | 2 (11%) |
| Other hypertension, n (%) | 19 | 0 |
| Asthma, n (%) | 19 | 1 (5%) |
| Thyroid disorder, n (%) | 19 | 4 (20%) |
| Depression, n (%) | 19 | 4 (20%) |
| Other (chronic lung, heart, immune, or hematologic disorders), n (%) | 19 | 0 |
| Vital signs | | |
| Blood pressure, systolic, mm Hg, median (IQR) | 19 | 117 (111–119) |
| Blood pressure, diastolic, mm Hg, median (IQR) | 19 | 73 (62–78) |
| Systolic ≥140 or diastolic ≥90 mm Hg, n (%) | 19 | 0 |
| Pulse, beats per min, median (IQR) | 19 | 79 (73–85) |
| Respirations, breaths per min, median (IQR) | 18 | 18 (16–20) |
| Temperature,°C, median (IQR) | 18 | 36.7 (36.5–36.9) |
| Temperature ≥38°C, n (%) | 18 | 1 (6%) |
| Oxygen % saturation, median (IQR) | 18 | 99 (98–100) |
| Oxygen saturation <95%, n (%) | 18 | 0 |
| Fetal cardiac activity absent | 19 | 5 (26%) |

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product transfusions were used in 95% of cases, usually with multiple units (median, 8 units; IQR, 3–14 units). Severe maternal morbidity included 6 patients transferred to the intensive care unit for hemodynamic support (all 6 received massive transfusions from 9–26 total units of blood products; 2 required ventilator support for 2 days each after peripartum hysterectomy). Median maternal total length of stay was 5 days for cesarean deliveries and 3 days for vaginal births, reflecting rapid resolution of DIC after delivery.

Placental histopathologic findings are summarized in Table 3. The narrative descriptions included several cases with some or all of the features of the SARS-CoV-2 placentitis triad: histiocytic intervillositis or similar descriptions, perivillous fibrin deposition, often described as severe or massive, and necrosis or infarction.

Newborn outcomes are summarized in Table 4. There were 18 singleton pregnancies and 1 twin pregnancy; therefore, the 19 patients delivered a total of 20 newborns, of which 13 were born alive (65%), and 7 were stillborn (35%), including 5 with fetal death on admission and 2 that occurred while under observation or while undergoing interfacility transfer. Autopsy was performed in 1 case; no external or internal abnormalities were noted. Comparing livebirths with stillbirths, the latency from COVID-19 diagnosis to admission was similar (median [IQR], 6 [4–8.5] vs 6 [4–9] days, respectively; $P$=.20). Of the 13 liveborn infants, Apgar scores were ≤5 in 85% at 1 minute and 54% at 5 minutes. Arterial cord blood gases were obtained in 9 cases, with pH ≤7.1 in 78% and base deficit ≥10 mEq/L in 75%, indicating metabolic acidosis. Newborn tests for COVID-19 were positive in 62% of liveborns. Neonatal complications included a high rate of respiratory distress syndrome (77%) and other morbidities typical for early preterm births. There were no neonatal deaths.

Table 5 compares selected observations between mothers with liveborn and those with stillborn neonates. Stillbirth cases presented a median of 3

**TABLE 1**
**Characteristics on admission** *(continued)*

| Characteristic | Number of observations | Result |
|---|---|---|
| Laboratory findings | | |
| White cell count, per mm$^3$, median (IQR) | 18 | 7.2 (6.2–8.4) |
| Hemoglobin, g/dL, median (IQR) | 18 | 12.9 (12.0–13.9) |
| Hematocrit, %, median (IQR) | 19 | 39 (36–43) |
| Platelet count, thousand per mm$^3$, median (IQR) | 19 | 58 (51–73) |
| Fibrinogen, mg/dL, median (IQR) | 15 | 81 (50–129) |
| Prothrombin time, s, median (IQR) | 17 | 14.1 (12.1–16.8) |
| International normalized ratio, median (IQR) | 15 | 1.1 (1.0–1.4) |
| Partial thromboplastin time, s, median (IQR) | 17 | 43.5 (41.0–53.8) |
| DIC criteria on admission | | |
| Platelet count ≤100,000 per mm$^3$, n (%) | 19 | 17 (89%) |
| Fibrinogen ≤200 mg/dL, n (%) | 15 | 12 (80%) |
| Prothrombin time prolonged ≥3 sec, n (%) | 14 | 4 (29%) |
| 2 or 3 of the above, n (%) | 19 | 17 (89%) |
| 3 of the above, n (%) | 19 | 2 (11%) |
| AST, IU/L, median (IQR) | 17 | 103 (83–160) |
| AST, fold elevated, median (IQR) | 16 | 2.5 (1.8–5.2) |
| AST elevated 1–2 times limit of normal, n (%) | 16 | 5 (31%) |
| AST elevated >2 times limit of normal, n (%) | 16 | 11 (69%) |
| ALT, IU/L, median (IQR) | 17 | 41 (25–52) |
| ALT, fold elevated, median (IQR) | 16 | 0.8 (0.6–1.3) |
| ALT elevated 1–2 times limit of normal, n (%) | 16 | 1 (6%) |
| ALT elevated >2 times limit of normal, n (%) | 16 | 3 (19%) |
| Serum bilirubin, mg/dL, median (IQR) | 15 | 0.5 (0.2–0.8) |
| Serum creatinine, mg/dL, median (IQR) | 16 | 0.63 (0.56–0.75) |

*ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *DIC*, disseminated intravascular coagulation; *IQR*, interquartile range.

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weeks earlier but were otherwise similar at presentation. Placental pathology was abnormal in all live births but normal in 3 of the stillbirths.

Table 6 compares the 19 cases who met all inclusion criteria with the 8 cases that were excluded because they did not meet our definition of DIC. Half of the excluded cases met the less-stringent DIC criteria of Erez et al,[33] whose scoring system gives points for less severe thrombocytopenia (platelet count <150,000/mm$^3$), hypofibrinogenemia (values <300 mg/dL), and prothrombin time prolongation (≥1.5 seconds) compared with our prespecified criteria based more closely on those of Clark et al.[32] The 2 groups were similar in gestational age at presentation and commonly presented with decreased fetal movement and were delivered by cesarean delivery on the day of admission. Laboratory findings were more often normal in the excluded group, which is expected because the reason for exclusion was insufficient severity of coagulation abnormalities. Transfusion rate was much lower in the excluded group. Rates of stillbirth and abnormal placental pathology were similar in both groups.

## Comment

### Principal findings

In this cohort of patients with DIC and otherwise mild or asymptomatic maternal COVID-19, common features were presentation in the late second or early third trimester with decreased fetal movement, nonreassuring fetal heart rate patterns triggering cesarean delivery soon after admission, high rates of severe maternal morbidity (postpartum hemorrhage, multiunit blood product transfusion, intensive care unit admission), high rates of perinatal morbidity (stillbirth, fetal metabolic acidosis), and placental histopathology with features of SARS-CoV-2 placentitis (histiocytic intervillositis, intervillous fibrin deposition, and necrosis).

### Results in the context of what is known

This was a relatively large case series of DIC in pregnant patients with COVID-19. We included cases from different regions of the United States and from time periods both before and during the surge of the B.1.617.2 (Delta) variant in late 2021. The study period specified by our protocol ended before the initial surge of the B.1.1.529 (Omicron) variant in early 2022.

Adverse maternal and perinatal outcomes of COVID-19 during pregnancy are typically increased in those with severe or critical maternal disease,[21,31,34] yet our DIC cohort had high rates of severe maternal morbidity and perinatal death despite otherwise clinically mild maternal COVID-19.

Several case reports have many similarities to our cases. The earliest described 2 cases at 35 weeks' gestation that had rapidly worsening maternal coagulopathy and were treated with multiunit transfusions, with delivery soon after admission; placental pathology was not described.[23] Another case presented at 36 weeks' gestation with decreased fetal movement and abnormal fetal heart rate tracing leading to cesarean delivery[26]; histopathology was consistent with SARS-CoV-2 placentitis. Immunohistochemistry for SARS-CoV-2 was strongly positive in the trophoblasts, and coagulation studies

were not reported. Another case presented at 31 weeks' gestation with decreased fetal movement, headache, malaise, cough, and dyspnea[27]; thrombocytopenia and elevated AST were noted. Emergency cesarean delivery was performed, and the mother was transfused with fibrinogen and 2 units of red cells. Placental histopathology showed histiocytic intervillositis and extensive perivillous fibrin; the fetal side of the placenta had positive immunostaining for SARS-CoV-2 and tested positive for SARS-CoV-2 RNA. Three additional cases were patients who tested positive for the SARS-CoV-2 Delta variant, presenting at 30 to 35 weeks' gestation, 2 with fetal death and 1 with category 3 tracing and DIC[28]; placentas showed SARS-CoV-2 placentitis, and RNA from placental biopsies was positive for the Delta variant.

DIC in pregnancy is often triggered by abnormal placental processes, including abruption, amniotic fluid embolism, and longstanding fetal death. The pathophysiology has been summarized as follows: "Any condition that disrupts the integrity of the trophoblast can lead to a release of a large amount of potent Tissue Factor that will activate the coagulation cascade and propagate an inflammatory response that can easily become systemic, leading to uncontrolled thrombin generation and the subsequent development of DIC."[35]

Placental histopathologic findings were reported in a series of 64 fetal deaths and 4 neonatal deaths in maternal COVID-19 cases whose placentas tested positive for SARS-CoV-2.[36] The triad of SARS-CoV-2 placentitis (histiocytic intervillositis, increased fibrin deposition, and trophoblast necrosis) was observed in 66 of 68 (97%) cases; the 2 remaining cases lacked only histiocytic intervillositis.

Our series suggests that SARS-CoV-2 placentitis may have degrees of severity and does not always result in fetal death. We had several liveborn cases with histopathologic features of the placentitis triad (Table 3). Perhaps these were delivered earlier in a process that would have progressed to fetal death if not for prompt intervention, or perhaps they

**TABLE 2**
**Maternal course and pregnancy outcomes**

| Characteristic | Number of observations | Result |
|---|---|---|
| Delivery timing | 19 | |
| Delivered on day of admission, n (%) | | 14 (74%) |
| Delivered day after admission, n (%) | | 5 (26%) |
| Gestational age at delivery | 19 | |
| Previable or periviable (<24 wk), n (%) | | 0 |
| Extremely preterm (24–$27^{6/7}$ wk), n (%) | | 4 (21%) |
| Very preterm (28–$31^{6/7}$ wk), n (%) | | 7 (37%) |
| Early preterm (32–$33^{6/7}$ wk), n (%) | | 4 (21%) |
| Late preterm (34–$36^{6/7}$ wk), n (%) | | 4 (21%) |
| Term, n (%) | | 0 |
| Delivery method | 19 | |
| Cesarean delivery, n (%) | | 13 (68%) |
| Spontaneous vaginal, n (%) | | 5 (26%) |
| Operative vaginal (breech extraction of stillborn fetus), n (%) | | 1 (5%) |
| Anesthesia for cesarean delivery | 13 | |
| General, n (%) | | 8 (62%) |
| Spinal, n (%) | | 4 (31%) |
| Epidural, n (%) | | 1 (8%) |
| Primary indication for delivery | 19 | |
| Abnormal fetal heart rate tracing, n (%) | | 12 (63%) |
| Fetal death, n (%) | | 6 (32%) |
| Bleeding, n (%) | | 1 (5%) |
| Postpartum hemorrhage | 19 | 9 (47%) |
| Treated with uterotonic agents more than oxytocin, n (%) | 9 | 6 (67%) |
| Treated with balloon tamponade, n (%) | 9 | 1 (11%) |
| Treated with hysterectomy, n (%) | 9 | 2 (22%) |
| Transfusion | | |
| Red cells, number of patients, n (%) | 19 | 12 (63%) |
| Fresh/frozen plasma, number of patients, n (%) | 19 | 15 (79%) |
| Cryoprecipitate, number of patients, n (%) | 19 | 17 (89%) |
| Platelets, number of patients, n (%) | 19 | 13 (68%) |
| Any blood product, n (%) | 19 | 18 (95%) |
| Total units of blood products given | 19 | 8 (3–14) |
| Treatments for COVID-19 | | |
| None, n (%) | 19 | 10 (53%) |
| Monoclonal antibodies, n (%) | 19 | 3 (16%) |
| Remdesivir, n (%) | 19 | 3 (16%) |
| Other, n (%) | 19 | 2 (11%) |

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*(continued)*

**TABLE 2**
**Maternal course and pregnancy outcomes** *(continued)*

| Characteristic | Number of observations | Result |
|---|---|---|
| Follow-up laboratory studies | | |
| Lowest platelet count, thousand per $mm^3$, median (IQR) | 19 | 52 (38–67) |
| Lowest fibrinogen, mg/dL, median (IQR) | 18 | 77 (50–96) |
| Longest prothrombin time, s, median (IQR) | 18 | 14.6(13.1–19.1) |
| Longest partial thromboplastin time, s, median (IQR) | 19 | 43.5 (41–53.8) |
| DIC criteria at any time during hospitalization | | |
| Platelet count ≤100,000 per $mm^3$, n (%) | 19 | 19 (100%) |
| Fibrinogen ≤200 mg/dL, n (%) | 18 | 18 (100%) |
| Prothrombin time prolonged ≥3 s, n (%) | 18 | 5 (28%) |
| 2 or 3 of above, n (%) | 19 | 19 (100%) |
| 3 of above, n (%) | 19 | 4 (21%) |
| Highest AST, median (IQR) | 18 | 111 (83–162) |
| Highest AST, fold elevated, median (IQR) | 16 | 3.0 (2.3–5.2) |
| Highest AST elevated 1–2 times limit, n (%) | 16 | 2 (12%) |
| Highest AST elevated >2 times limit, n (%) | 16 | 14 (88%) |
| Highest ALT | 18 | 44 (29–85) |
| Highest ALT, fold elevated | 16 | 0.8 (0.7–2.4) |
| Highest ALT elevated 1–2 times limit, n (%) | 16 | 2 (12%) |
| Highest ALT elevated >2 times limit, n (%) | 16 | 4 (25%) |
| Maternal complications | | |
| Death, n (%) | 19 | 0 |
| Admission to intensive care unit, n (%) | 19 | 6 (32%) |
| Intubation for mechanical ventilation, n (%) | 19 | 2 (11%) |
| Ventilator days, median (IQR) | | 2 (2–2) |
| Bleeding complications | 19 | |
| Postpartum hemorrhage, n (%) | | 9 (47%) |
| Gastrointestinal bleeding, n (%) | | 1 (5%) |
| Other bleeding, n (%) | | 1 (5%) |
| Venous or pulmonary thromboembolism, n (%) | 19 | 0 |
| Shock, n (%) | 19 | 2 (11%) |
| Multiorgan failure, n (%) | 19 | 0 |
| Chorioamnionitis, n (%) | 19 | 1 (5%) |
| Positive blood culture, n (%) | 4 | 0 |
| Maternal total length of stay (d) | | |
| All patients, median (IQR) | 19 | 4 (3–6) |
| Cesarean deliveries, median (IQR) | 13 | 5 (4–7) |
| Vaginal deliveries, median (IQR) | 6 | 3 (3–3) |

*ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *IQR*, interquartile range.

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were simply milder cases. Furthermore, the placental pathology in 3 of our stillbirth cases was described as normal, suggesting unidentified nonplacental causes of DIC and stillbirth in some cases.

SARS-CoV-2 placentitis shares some histopathologic features with the syndrome of massive perivillous fibrin deposition (MPFD, also known as maternal floor infarction), a rare condition with diverse causes (immune, metabolic, viral), associated with high risk of miscarriage, fetal growth restriction, and fetal death.[37–39] It has been hypothesized that MPFD is a response to trophoblast injury.[39] However, MPFD seems distinct from SARS-CoV-2 placentitis in that it typically lacks histiocytic intervillositis and trophoblast necrosis and is not typically associated with DIC. Furthermore, MPFD usually has a chronic or indolent course, explaining its association with fetal growth restriction, whereas our cases had acute onset and rapid course.

Stillbirth is uncommon among COVID-19 pregnancies. A multicenter study of 2352 pregnancies with COVID-19 in 2020 (before the Delta surge) did not find a significantly higher rate of stillbirth compared with 11,752 pregnancies without COVID-19 (0.5% vs 0.7%, respectively).[21] However, CDC surveillance data[40] showed that maternal COVID-19 was associated with a relative risk of stillbirth of 1.47 (95% confidence interval, 1.27–1.71) before July 2021 (pre-Delta) compared with 4.04 (95% confidence interval, 3.28–4.97) from July to September 2021 (during the Delta surge). However, despite the high relative risk during the Delta surge, the absolute stillbirth rate among maternal COVID-19 cases was 2.70%, much lower than the 35% observed in our cohort, with similar frequency before and during the Delta surge (Table 5).

Considered in context with literature reports, our findings suggest that maternal COVID-19 may uncommonly trigger a triad of complications that includes placentitis, DIC, and fetal compromise. These do not necessarily occur in an all-or-none fashion; many cases

**TABLE 3**
**Placental pathology findings**

| Delivery gestational age, wk.d | Neonatal birth status | Placental pathology conclusion | Pathology report excerpt |
|---|---|---|---|
| 24.5 | Stillborn | Abnormal | Diffuse chronic histiocytic intervillositis with marked increased intervillous fibrin deposition. |
| 27.2 | Stillborn | Normal | |
| 27.4 | Alive | Abnormal | Diffuse acute and organizing intervillositis. |
| 27.4 | Alive | Abnormal | Prominent perivillous fibrin deposition. Prominent chronic intervillositis. No chorioamnionitis. |
| 28.5 | Stillborn | Abnormal | Chronic histiocytic intervillositis with increased perivillous fibrin deposition |
| 29.0 | Stillborn | Abnormal | Massive perivillous fibrin deposition involving >70% of maternal surface and placental parenchymal involvement. |
| 29.0 | Alive | Abnormal | Chronic histiocytic intervillositis with increased perivillous fibrin deposition. |
| 29.2 | Stillborn | Normal | |
| 29.6 | Stillborn | Normal | |
| 30.1 | Alive | Abnormal | Diffuse and severe perivillous inflammation (histiocytic and neutrophilic) with synctiotrophoblastic membrane necrosis and diffuse perivillous fibrin deposition. Multifocal chorioangiosis. Focal stem vessel sclerosis. |
| 31.5 | Alive | Not done | |
| 32.4 | Alive | Abnormal | Marked increase in perivillous fibrin deposition and increased intervillous histiocytes. |
| 32.5 | Alive | Not done | |
| 33.2 | Stillborn | Abnormal | Massive perivillous fibrin deposition, chronic histiocytic intervillositis, near total villous infarction. |
| 33.6 | Alive | Abnormal | 30% of placenta: multiple early subacute infarcts. |
| 34.3 | Alive | Abnormal | Focally increased subchorionic fibrin, areas with dystrophic calcification, increased perivillous fibrin, histiocytic intervillositis. Diamniotic-dichorionic twin placenta. No significant inflammation. |
| 35.1 | Alive | Abnormal | Perivillous fibrin with subacute villous infarction involving >50% of placental parenchyma, irregular villous maturation, patchy villous hypervascularity, mild ischemic change. |
| 35.4 | Alive | Abnormal | Markedly increased intervillous fibrin deposition. Villous stromal-vascular karyorrhexis plus chronic villitis. |
| 36.6 | Alive | Abnormal | Chronic histiocytic intervillositis, massive perivillous fibrin deposition. |

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had some of these manifestations but not others. For example, in our 8 excluded cases with only 1 coagulation abnormality, there were still high rates of decreased fetal movement, stillbirth, positive neonatal SARS-CoV-2 testing, and abnormal placental pathology. We do not know whether some patients with otherwise mild COVID-19 develop placentitis and DIC because of a genetic predisposition, gestational age–dependent variations in placental expression of SARS-CoV-2 receptors,[41–43] or other factors.

Some of the features of COVID-19-associated DIC overlap with the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, a variant of severe preeclampsia. COVID-19 is associated with 2-fold increased risk for HELLP syndrome and other forms of preeclampsia and eclampsia.[44] However, all of our patients had normal blood pressure on admission, and only 2 had signs of preeclampsia other than thrombocytopenia or transaminase elevation (Table 1). Furthermore, it is rare for HELLP syndrome to be associated with hypofibrinogenemia or prolonged prothrombin time. The observation that serum AST was always elevated, whereas ALT was usually normal, suggests an extrahepatic source of AST.[45]

## Clinical implications

The first principle of treatment for DIC is to remove or manage the underlying cause,[35] presumably the placenta. Prompt delivery in our cases was followed by rapid resolution of DIC and favorable maternal outcomes. The

**TABLE 4**
**Neonatal outcomes**

| Characteristic | Number of observations | Result |
|---|---|---|
| Birthweight, g, median (IQR) | 20 | 1530 (1063–2022) |
| Birthweight <10th percentile, n (%) | | 1 (5%) |
| Birthweight >90th percentile, n (%) | | 1 (5%) |
| Status at birth | 20 | |
| Liveborn, n (%) | | 13 (65%) |
| Stillborn, n (%) | | 7 (35%) |
| Apgar score in liveborn infants | | |
| At 1 min, median (IQR) | 13 | 1 (1–2) |
| Score ≤5 at 1 min, n (%) | 13 | 11 (85%) |
| At 5 min, median (IQR) | 13 | 5 (4–8) |
| Score ≤5 at 5 min, n (%) | 13 | 7 (54%) |
| Umbilical cord blood gases in liveborn infants | | |
| Arterial pH, median (IQR) | 9 | 7.06 (7.00–7.10) |
| Arterial pH ≤7.1, n (%) | 9 | 7 (78%) |
| Arterial base deficit, median (IQR) | 8 | 17.7 (11.3–20.3) |
| Arterial base deficit ≥10, n (%) | 8 | 6 (75%) |
| Laboratory studies in liveborn infants | | |
| Admission hemoglobin, median (IQR) | 13 | 17.3 (16.4–17.8) |
| Admission hematocrit, median (IQR) | 13 | 52 (45–54) |
| Platelet count, 1000 per $mm^3$ | | |
| Admission, median (IQR) | 13 | 238 (199–255) |
| Lowest, median (IQR) | 13 | 198 (110–247) |
| Lowest <100,000 per $mm^3$, n (%) | 13 | 3 (23%) |
| SARS-CoV-2 test result | 13 | |
| Positive, n (%) | | 8 (62%) |
| Negative, n (%) | | 3 (23%) |
| Not tested, n (%) | | 2 (15%) |
| Complications in liveborn infants | | |
| Congenital anomaly, n (%) | 13 | 0 |
| Respiratory distress syndrome, n (%) | 13 | 10 (77%) |
| Bronchopulmonary dysplasia, n (%) | 12 | 1 (8%) |
| Pneumonia, n (%) | 13 | 2 (15%) |
| Pneumothorax, n (%) | 13 | 1 (8%) |
| Intraventricular bleeding | 13 | |
| Grade 1 or 2, n (%) | | 4 (31%) |
| Grade 3, n (%) | | 3 (23%) |
| Periventricular leukomalacia, n (%) | 13 | 0 |

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*(continued)*

second principle is supportive care with blood product replacement as needed. Most maternity hospitals now have a massive transfusion protocol that should make readily available multiple units of red cells, platelets, and fibrinogen (as fresh/frozen plasma or cryoprecipitate). In DIC, these products may be consumed rapidly, thus periodic reassessment and repeated transfusion may be required. Anticoagulation is relatively contraindicated until the risk of hemorrhage has decreased.[35]

There is no standardized protocol for maternal–fetal surveillance after maternal COVID-19 diagnosis. Clinicians typically find it reassuring if patients are mildly symptomatic or asymptomatic. After pregnant patients test positive for SARS-CoV-2, routine visits for prenatal care, ultrasound examinations, and fetal surveillance are often postponed to minimize potential exposure of noninfected persons. However, we recommend that COVID-19 patients who report decreased fetal movement be promptly evaluated at a hospital because this was the most frequently reported symptom in our cohort. If the fetal heart rate pattern is nonreassuring, we recommend checking at minimum a complete blood count, prothrombin time, and fibrinogen, even if the patient is otherwise asymptomatic. A diagnosis of DIC has profound implications for subsequent patient management, including ordering of blood products, avoidance of neuraxial anesthesia, and anticipation of hemorrhage.

## Research implications

Future study is needed to elucidate maternal risk factors for DIC and SARS-CoV-2 placentitis and to test whether therapeutics such as monoclonal antibodies or antiviral medications can decrease the risk of developing DIC or mitigate its course. Long-term follow-up of these cases is needed to understand whether there is a risk for related problems in subsequent pregnancies or long-term maternal or neonatal health risks. Future studies should also address the incidence of these complications among COVID-19-affected gravidas as new variant strains come to predominate. Per our

**TABLE 4**
**Neonatal outcomes** *(continued)*

| Characteristic | Number of observations | Result |
|---|---|---|
| Retinopathy of prematurity | 12 | |
| Stage 1 or 2, n (%) | | 2 (17%) |
| Stage 3, n (%) | | 1 (8%) |
| Necrotizing enterocolitis, n (%) | 13 | 0 |
| Sepsis, n (%) | 13 | 0 |
| Days in hospital for liveborn infants, median (IQR) | 13 | 29 (18–52) |
| Days in neonatal intensive care unit, median (IQR) | 13 | 29 (18–37) |
| Status on discharge of liveborn infants | 13 | |
| Alive to home, n (%) | | 12 (92%) |
| Transferred alive to another facility, n (%) | | 1 (8%) |
| Neonatal death, n (%) | | 0 |

*IQR*, interquartile range.

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approved protocol, we stopped collecting cases at the end of 2021, just as the B.1.1.529 (Omicron) surge was starting.

## Strengths and limitations

Strengths of the study include capture of extensive clinical data for each case. Using social media, we were able to rapidly identify cases from across the United States. Although this was a relatively large series of COVID-19-related DIC, the number of cases was small.

Limitations include those inherent to retrospective observational studies. The study design did not allow inferences on the incidence of DIC or placentitis among COVID-19 pregnancies because we did not know the overall time- and location-specific prevalence rates of the disease in the included populations. Some data were missing from the medical records. As an exclusion criterion, our definition of severe COVID-19 based on ventilator support or ECMO differed from the National Institutes of Health definition,[46] which is based on arterial blood gas values, chest imaging, and respiratory rate; although we did not collect data on blood gas values, none of our included cases had oxygen saturation <95% on pulse oximetry, and only 1 had a respiratory rate >30 breaths per minute on admission. We did not specify a standardized definition of nonreassuring fetal heart rate pattern and relied instead on the judgment of the treating physicians. Placental histopathology evaluations and nomenclature were not standardized, which is a well-known limitation of placental pathology in multicenter studies[47]; we did not collect data regarding whether the hospital pathologists had specialized training in placental histopathology. We did not have data on SARS-CoV-2 subtype or viral load because such

**TABLE 5**
**Factors associated with stillbirth**

| Factor | Liveborn N=12 | Stillborn N=7 | *P* value |
|---|---|---|---|
| Gestational age at admission, wk | 32.4 (29.6–34.7) | 29.0 (27.2–29.6) | .04 |
| Maternal age, y | 34 (31–36) | 28 (26–32) | .06 |
| Month of presentation | | | .66 |
| Oct 2020–June 2021 | 4 (67%) | 2 (33%) | |
| July 2021–Dec 2021 | 9 (64%) | 5 (36%) | |
| Admission laboratory values | | | |
| Platelet count, 1000 per $mm^3$ | 67 (44–90) | 58 (51–63) | .33 |
| Fibrinogen, mg/dL | 66 (50–112) | 82 (80–129) | .32 |
| Aspartate aminotransferase, IU/L | 112 (91–182) | 85 (63–106) | .20 |
| Admission blood pressure | | | |
| Systolic, mm Hg | 117 (108–120) | 117 (114–118) | .86 |
| Diastolic, mm Hg | 74 (65–78) | 73 (62–79) | 1.00 |
| Abnormal placental pathology | 10/10 (100%) | 4/7 (57%) | .04 |

Data are median (interquartile range) or number (percentage). *P* values from *U*-test or chi-square test.

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**TABLE 6**
**Comparison of included vs excluded cases**

| Factor | Included cases N=19 | Excluded cases N=8 | *P* value |
|---|---|---|---|
| Gestational age at admission, wk | 30.1 (28.5–33.6) | 27.5 (24.7–32.7) | .23 |
| Maternal age, y | 31 (27–35) | 30 (25–33) | .61 |
| Decreased fetal movement | 11/19 (58%) | 5/8 (63%) | .82 |
| Twin pregnancy | 1/19 (5%) | 1/8 (13%) | .51 |
| Delivered on day of admission | 14/19 (74%) | 6/8 (75%) | .94 |
| Cesarean delivery | 13/19 (68%) | 4/8 (50%) | .37 |
| Stillbirth | 7/20 (35%) | 4/9(44%) | .69 |
| DIC criteria | | | |
| Platelet count ≤100,000 per $mm^3$ | 19/19 (100%) | 1/8 (12%) | n/a[a] |
| Fibrinogen ≤200 mg/dL | 18/19 (95%) | 4/8 (50%) | n/a[a] |
| Prothrombin time prolonged ≥3 s | 5/19 (26%) | 0/8 (0%) | n/a[a] |
| ≥2 of above (our definition of DIC) | 19/19 (100%) | 0/8 (0%) | n/a[a] |
| ISTH pregnancy-modified DIC score | 27 (26–51) | 25 (25–27) | n/a[a] |
| Score ≥26 (their definition of DIC) | 19/19 (100%) | 4/8 (50%) | n/a[a] |
| Most abnormal laboratory values | | | |
| Platelet count, 1000 per $mm^3$ | 52 (28–37) | 209 (121–326) | n/a[a] |
| Fibrinogen, mg/dL | 77 (50–96) | 182 (152–229) | n/a[a] |
| Prothrombin time, s | 14.6 (13.1–19.1) | 10.7 (10.2–10.8) | n/a[a] |
| Aspartate aminotransferase, IU/L | 110 (83–162) | 50 (41–61) | n/a[a] |
| Elevated times upper limit | 3.0 (2.3–5.2) | 1.4 (1.0–2.4) | n/a[a] |
| Blood product transfusion, total units | 8 (3–4) | 0 (0–3) | .002 |
| Abnormal placental pathology | 14/17 (82%) | 7/8 (88%) | .71 |
| Newborn positive test for COVID-19 | 8/11 (72%) | 1/4 (25%) | .58 |

Data are median (interquartile range) or number (percentage). *P* values from *U*-test or chi-square test.

*DIC*, disseminated intravascular coagulation; *ISTH*, International Society on Thrombosis and Haemostasis, score from Erez et al.[33]

[a]Statistical test not applicable because groups are defined by laboratory values.

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testing is not routinely performed for hospitalized COVID-19 patients. Viral testing was not reported for any of the stillborn fetuses. Placentas were not tested for SARS-CoV-2 by either direct tests or specific immunohistochemistry. The positive neonatal tests for SARS-CoV-2 were not definitive evidence of vertical transmission because we did not capture details about specimen source or timing of the tests; furthermore, there are no standardized criteria to define vertical transmission of SARS-CoV-2. We were not able to determine whether respiratory illness in the affected neonates was caused by SARS-CoV-2 or by prematurity. Finally, the small sample size yielded low statistical power for inferential statistical testing.

## Conclusions

Some patients with COVID-19 in pregnancy develop placentitis and DIC with severe fetal compromise or fetal death, despite having only mild or asymptomatic maternal disease. Clinicians should be alert to this uncommon but serious presentation and prepare for prompt delivery, postpartum hemorrhage, and multiunit blood product transfusion. ■

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