





Obstetrics

COVID-19-associated coagulopathy and unfavorable obstetric outcomes in the third trimester of pregnancy

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Bleeding and clotting disorders⁴ occurring in patients with a SARS-CoV-2 infection have been defined as "COVID-19-associated coagulopathy" (CAC).¹ Thrombosis caused by SARS-CoV-2 appears to occur in an indirect way, which includes all three components of Virchow's triad.² Initial CAC presents with elevation of D-dimer (DD) and increased serum fibrinogen, while prothrombin time, partial thromboplastin time, and platelet counts either change minimally or not at all.³

Between December 2020 and May 2021, 3138 pregnant women were admitted to our obstetric unit, the largest high-risk maternity unit in the metropolitan area of Milan, Italy, for antenatal care. A total of 184 patients (5.9%) tested positive for SARS-CoV-2 infection, and, amongst these, 3 (1.6%) presented with CAC. The characteristics of the women diagnosed with CAC are shown in Table 1.

All three women had a diagnosis of fetal growth restriction and all cases were characterized by rapid onset of obstetric complications subsequent to admission, which occurred due to reduced fetal movements. None of the women required intensive care.

In Case 1, a sonographic scan revealed massive placental abruption, leading to an emergent cesarean section. The newborn was male, weighed 1009 g, and died after numerous attempts at resuscitation. In Case 2, cardiotocography detected persistent severe fetal bradycardia (around 70 bpm) and the patient underwent an emergent cesarean section. The newborn was male, weighed 790 g, and died after numerous attempts at resuscitation. In Case 3, fetal cardiotocography at admission was category II (according to ACOG

guidelines)⁴ and an emergency cesarean section was performed. The newborn was a female and weighed 1745 g, Apgar score at 1 and 5 min was 6 and 8, respectively, and pH measured in the umbilical artery was 7.23.

The authors hypothesize that the systemic endothelial damage caused by SARS-CoV-2 infection may have played a synergic role with the vascular dysfunction connected to growth restriction. This resulted in exacerbation of placental oxidative stress and consequent endothelial damage, leading to unfavorable obstetric complications.

The hypercoagulable state of pregnancy predisposes women to an increased thromboembolic risk, which is most exacerbated during the third trimester, especially in women with a SARS-CoV-2 infection.

Therefore, special attention should be reserved to women with altered fibrinogen, DD, and platelet levels, regardless of whether they have asymptomatic or mild SARS-CoV-2 infection. Close maternal and fetal monitoring is needed and an early delivery should be considered if necessary in order to minimize unfavorable outcomes.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the conception, planning, carrying out and analysis of the manuscript. GEC and FD were the primary writers of the manuscript. All authors read, revised and consented to the publication of the final version of the manuscript.

TABLE 1 Maternal fetal characteristics and pregnancy outcomes

	Case 1	Case 2	Case 3
Age (year)	37	32	26
Ethnicity	Latin American	Caucasian	Caucasian
Gestational age at time of admission (wk)	28	27	32
Medical history	Negative	Negative	Negative
Obstetric history	Primigravida	Primigravida	Previous pregnancy complicated by IUGR
Pregnancy complications	- IUGR - Cerebroplacental ratio <5 percentile - Doppler velocimetry of both uterine arteries - Pulsatility index >95	- IUGR - Cerebroplacental ratio <5 percentile - Doppler velocimetry of both uterine arteries - Pulsatility index >95	- IUGR - Normal cerebroplacental ratio - Normal Doppler velocimetry of both uterine arteries
Timing of COVID-19 diagnosis	Previous to admission to hospital (during third trimester)	Previous to admission to hospital (during third trimester)	Previous to admission to hospital (during third trimester)
Severity of COVID-19 symptoms at time of admission	Mild infection	Mild infection	Mild infection
Patient's vital signs at time of admission	Normal	Normal	Normal
Reason for hospital admission	Reduced fetal movements	Reduced fetal movements	Reduced fetal movements
Blood tests at time of admission	- Reduced hemoglobin and fibrinogen - Increased DD	- Thrombocytopenia - Decreased fibrinogen and increased levels of DD - CRP was slightly increased	- Thrombocytopenia - Increased DD, transaminases and LDH - Slight increase in CRP - Low fibrinogen
Pregnancy outcome	- Abruptio placentae 12 h following admission - Emergent cesarean section and fetal demise	Severe fetal bradycardia - Emergent cesarean section and fetal demise	- Type 2 fetal cardiotocography - Emergency cesarean section - Viable fetus
Time before normalization of blood tests (h)	48	48	6
Histological examination of the placenta	- Fibrin deposits - Microcalcifications - Signs of chronic hypoxia	- High grade villitis - Fibrin deposits - Microcalcifications	- Fibrin deposits - Microcalcifications - Signs of chronic hypoxia

Abbreviations: CRP, C-reactive protein; DD, D-dimer; IUGR, intrauterine growth restriction; LDH, lactate dehydrogenase.

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