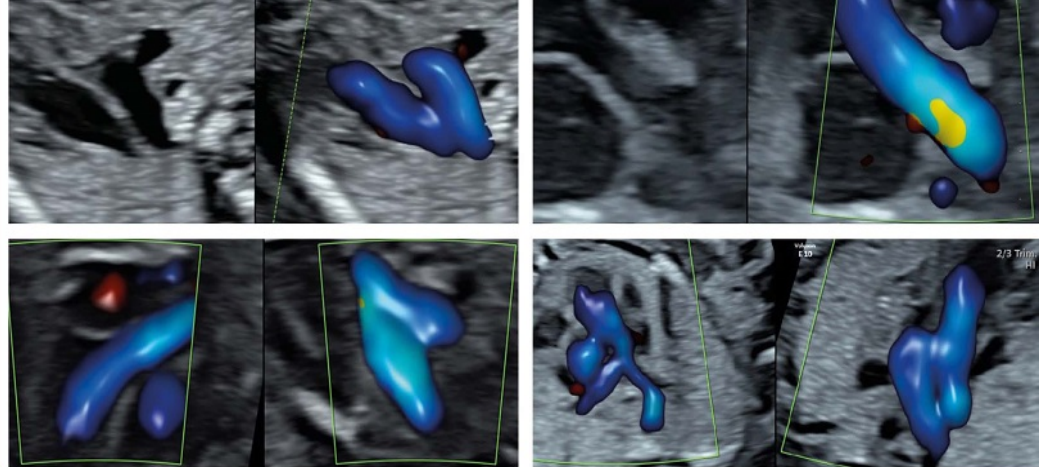


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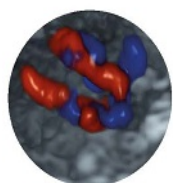
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Letters to the Editor

Pregnancies recovered from SARS-CoV-2 infection in second or third trimester: obstetric evolution

Since December 2019, the world has been impacted by COVID-19, caused by the virus SARS-CoV-2. This disease can affect the entire population, with the oldest and those with comorbidities being the most severely affected. During the first 7 months of the COVID-19 outbreak, findings have been reported in thousands of affected pregnant women, which has allowed us to gain an understanding of the effects of SARS-CoV-2 infection in pregnancy^{1,2}. We have learned that the risk of complication, hospitalization, admission to the intensive care unit and need for ventilation is greater in pregnant women with COVID-19 than in non-pregnant affected adults. Increased rates of Cesarean section, premature birth, prelabor rupture of the membranes (PROM) and other obstetric complications have been found to be associated with COVID-19^{1,2}. However, the maternal and perinatal outcomes of continuing pregnancies that have recovered from maternal SARS-CoV-2 infection are as yet unknown.

We analyzed data from pregnant women with symptoms of COVID-19 and positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 between 8 March and 15 August 2020, who later recovered, as determined by negative clinical assessment or RT-PCR at least 35 days after the onset of symptoms, delivered at one of four hospitals in the Republic of Panama (Complejo Metropolitano de la Caja de Seguro Social, Hospital Santo Tomás, Hospital Luis “Chicho” Fabrega and Hospital José Domingo De Obaldía). All women provided signed consent. The study was approved by the national bioethics committee (protocol reference: EC-CNBI-2020-04-45).

Table 1 shows the findings of the 15 participating patients, including one twin pregnancy. In 10 (66.7%) pregnancies, the diagnosis was made during the second trimester, and in five (33.3%) it was made in the third trimester. There were three severe cases and two required mechanical ventilation for more than 1 week, but these pregnancies continued for more than 10 weeks after diagnosis. Three pregnancies were complicated by PROM, occurring very preterm in two cases. Only four pregnancies reached 39 weeks; the others did not due to obstetric complication or spontaneous onset of labor. Five neonates were admitted to the neonatal intensive care unit. There were three perinatal deaths, of which one occurred intrauterine without an apparent cause and two occurred postnatally due to prematurity.

This first report of pregnant women infected with SARS-CoV-2 with subsequent recovery demonstrates that these patients continue to be at high obstetric risk, especially due to PROM and labor before 39 weeks. These pregnancies should be monitored closely until delivery. Eleven of the 15 (73.3%) patients in this series presented with PROM, spontaneous labor or maternal complication before 39 weeks of gestation, and only one out of 10 (10.0%) women diagnosed in the second trimester reached 39 weeks of gestation. These findings are of concern as they suggest the possibility of chronic inflammation with alteration at the placental or membrane level, triggering the culmination of pregnancy.

A study of 16 placentas from COVID-19 patients reported an increase in the rates of maternal and fetal vascular malperfusion features, as compared with controls. Two cases delivered more than 30 days after the onset of symptoms and these placentas showed fetal vascular malperfusion (clustered avascular villi, hypercoiled umbilical cord and chorangiosis)³. The possible inflammatory effect at the uterine or placental level in patients with COVID-19 has also been suggested as an explanation for excessive uterine activity reported in the cardiotocographic trace⁴ and for intrauterine death⁵.

More research is needed in pregnant patients recovered from COVID-19, and such studies should include analysis of placentas according to the recovery time, in order to obtain more information to guide follow-up and counseling of these patients. In our opinion, in pregnant patients recovered from SARS-CoV-2 infection, there is a ‘placental inflammatory syndrome’ characterized by spontaneous onset of labor, premature birth, PROM, alteration in the cardiotocographic trace, fetal distress, perinatal death and placental changes.

Undoubtedly, alteration of the mother’s state of health during pregnancy caused by SARS-CoV-2 infection can have long-term effects on the health of offspring, which seem to originate from the placenta.

It is interesting to note that most of the patients had some comorbidity. At this stage, we cannot be sure if this is characteristic of the majority of pregnant women infected with SARS-CoV-2 in Panama. However, the included pregnancies represent, at the time of writing, all those that had recovered and continued pregnancy for at least 5 weeks after initial symptoms.

In conclusion, the findings from this series of cases show that pregnant women who have recovered from COVID-19 remain at high obstetric risk, especially due to prematurity. Gestational age at the time of diagnosis of the disease will largely determine the prognosis, and a possible placental inflammatory syndrome is responsible for the perinatal side effects.

Table 1 Summary of maternal characteristics, symptoms and delivery details in 15 pregnancies that recovered from second- or third-trimester maternal SARS-CoV-2 infection

Case	Age (years)	Symptoms	Severity	GA at diagnosis (weeks)	GA at delivery (weeks)	Symptom onset-to-delivery interval (days)	Maternal comorbidity	Mode of delivery	Birth weight (g)	NICU admission	Observations
1*	20	Cough, SoB	Mild	20+6	28+0	50	PROM	CS	855, 955	Yes (both)	Premature delivery 26 days after PROM, both twins died at 3 weeks
2	24	Fever, cough	Mild	23+4	34+3	76	Obesity	Vaginal	2840	No	SOL
3	22	Headache, runny nose	Mild	28+6	37+1	58	Obesity, PROM	CS	3110	No	SOL
4	22	Fever, cough	Severe†	26+4	37+6	79	Obesity	Vaginal	2605	No	FGR, mother admitted to ICU for 10 days
5	26	Fever, cough	Mild	26+4	34+0	52	PROM	Vaginal	2439	Yes	Premature delivery 50 days after PROM
6	35	Anosmia	Mild	33+0	39+5	47	CH, obesity	CS	3336	No	—
7	29	Fever, SoB	Severe†	27+3	37+6	73	Obesity	CS	3720	No	Mother admitted to ICU for 10 days, SOL
8	36	Fever, cough	Mild	25+2	37+3	85	PE	Vaginal	3190	No	—
9	23	Fever, headache, runny nose	Mild	34+2	40+2	42	Obesity	CS	3434	No	—
10	22	Fever	Mild	31+1	36+1	35	Obesity	Vaginal	2749	No	SOL
11	33	Headache, runny nose, anosmia	Mild	22+3	28+1	40	—	CS	960	No	Died <i>in-utero</i> with no apparent cause
12	35	Fever, headache, SoB	Severe	18+2	30+5	87	Overweight	CS	1150	Yes	Premature
13	23	Fever, cough, headache	Mild	34+0	40+5	47	Obesity	Vaginal	3511	No	—
14	23	Fever, headache, runny nose	Mild	22+5	28+5	42	PE	CS	1311	Yes	Premature
15	28	Runny nose, sore throat	Mild	25+0	40+0	105	Overweight	Vaginal	3120	No	—

*Twin pregnancy. †Admitted to intensive care unit (ICU). CH, chronic hypertension; CS, Cesarean section; FGR, fetal growth restriction; GA, gestational age; NICU, neonatal intensive care unit; PE, pre-eclampsia; PROM, prelabor rupture of membranes; SoB, shortness of breath; SOL, spontaneous onset of labor.

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