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# COVID-19 during pregnancy: non-reassuring fetal heart rate, placental pathology and coagulopathy

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## **Abstract**

A case of a pregnant woman suffering from COVID-19 is presented, who developed coagulopathy in the absence of severe clinical symptoms. The PCR test of the vaginal swab was positive on SARS-CoV-2 RNA, suggesting a possibility of perinatal transmission. A cesarean delivery was done because of a non-reassuring fetal heart rate; the placenta showed increased perivillous fibrin deposition and intervillitis. Moreover, placental infection with SARS-CoV-2 was demonstrated by placental immunostaining. We suggest a relation between placental fibrin deposition and both chronic and acute intervillitis, non-reassuring fetal heart rate and coagulopathy in pregnant women with COVID-19.

## Case Report

A 27-year old woman (gravida 2, para 1) presented to the obstetrical outpatient clinic at a gestational age (GA) of 31<sup>+4</sup> weeks, with complaints of headache, malaise, coughing, shortness of breath since ten days, fever and decreased fetal movements. She had a history of well-controlled type 1 diabetes with low-dose insulin, and pre-eclampsia in her previous pregnancy. She used prophylactic acetylsalicylic acid 1dd 80 mg. Her Body Mass Index was 22.4 kg/m<sup>2</sup>.

Her vital signs were normal; respiratory rate 15 breaths per minute, peripheral oxygen saturation (SpO<sub>2</sub>) 98%, blood pressure (BP) 142/76 mmHg, heart rate (HR) 105 beats per minute (bpm) and temperature 37.6 °C. The cardiotocography (CTG) showed fetal tachycardia of 165 bpm, but no additional abnormalities. The estimated fetal weight (2051 grams, 78<sup>th</sup> percentile) and the amount of amniotic fluid were normal. Her laboratory results showed signs of infection (Table 1).

She was admitted for fetal and maternal monitoring and cared for in isolation. COVID-19 was confirmed by a positive nasopharyngeal SARS-CoV-2 RNA PCR test, which was done using primers and probes as described by Corman et al. <sup>1</sup>

At a GA of 31<sup>+5</sup>, despite absence of clinical symptoms and normal vital signs, she developed thrombocytopenia, anemia and increased LD and ALT. HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) was rejected due to normal urate and haptoglobin levels. Disseminated intravascular coagulation (DIC) was suspected. A (partial) placental abruption as the cause of DIC was deemed unlikely because of absence of symptoms, and normal clinical examination, CTG and placental ultrasound evaluation. There were no signs of any bacterial superinfection. Corticosteroids were administered. The PCR

test of the vaginal swab on SARS-CoV-2 RNA turned out positive. Group B streptococcus was not detected in a rectovaginal swab.

At a GA of 32<sup>+1</sup> weeks, the CTG showed a decrease in variability and an incidental deceleration. The patient did not report any symptoms and had normal vital signs. Ultrasound examination showed oligohydramnios. The umbilical arterial Doppler was normal (pulsatility index: 0.8). Premature preterm rupture of membranes was suspected based on a fern-like pattern in a vaginal swab.

An emergency cesarean delivery (CD) was performed. The total blood loss was 1370cc. Three units of FFP, two grams of Fibrinogen, and two units of red blood cells were administered. The patient had a swift recovery and was discharged from the hospital two days postoperatively.

A neonate of 1920 grams (58<sup>th</sup> percentile) was born with Apgar scores 3, 6 and 10 after 1, 5 and 10 minutes. Arterial and venous umbilical cord pH values were 7.28 and 7.29, with corresponding base excess values of -4.9 mmol/L and -5.0 mmol/L. The baby was admitted at the neonatal intensive care unit in isolation. Both mother and father visited the baby only 72 hours after resolution of all COVID-19 associated complaints.

Empirical antibiotics could be stopped after 48 hours in the absence of signs of infection. PCR tests on neonatal nasopharyngeal swabs (day four and seven) on SARS-CoV-2 RNA were negative. The baby had an uneventful course and was discharged from the hospital after 31 days.



The placenta was macroscopically highly abnormal. The parenchyma showed an increase in perivillous fibrin (>30-40%); extending from the chorionic plate to the decidua. The intervillous space was reduced by 30-50%. Possible elements of infarction were seen. The villi were clumped together and trophoblast tissue was often no longer visible; consistent with fibrin depositions leading to trophoblast necrosis. Additionally, an extensive intervillitis without villitis was noted. The intervillitis had a chronic (histiocytes) and acute component (granulocytes). Fetal thrombotic vasculopathy or microthrombi were not seen. In the small spared areas there was increased maturation with terminal villi already forming (Figure 1). There was no sign of chorioamnionitis. A PCR test of the swab of the fetal side of the placenta tested positive on SARS-CoV-2 RNA. The presence of SARS-CoV-2 immunoreactive cells (trophoblasts and stromal cells) was observed after immunostaining.

## Discussion

Given the observed positive vaginal SARS-CoV-2 PCR test, as well as the placental infection with SARS-CoV-2, it could be suggested that perinatal transmission is possible. In the abovementioned case, premature preterm rupture of membranes was diagnosed prior to CD. The neonate may thus have been exposed to SARS-CoV-2 RNA present in the vagina. However, the neonate tested negative on SARS-CoV-2 RNA.

Multiple studies evaluated the risk of perinatal transmission by testing of the placenta, vaginal secretion, cord blood and amniotic fluid on SARS-CoV-2. The results of all samples obtained in these studies were negative for SARS-CoV-2.<sup>2-4</sup> Up to now, only one case report demonstrates transplacental transmission, while others suggest vertical transmission without compelling evidence.<sup>5,6</sup> In the abovementioned case, in the abnormal areas of the placenta the trophoblast tissue had mostly disappeared. Placental immunostaining demonstrated placental infection with SARS-CoV-2, but in view of the negative neonatal test results and the absence of signs of infection, no transmission had taken place. Moreover, there was no sign of chorioamnionitis.

Signs of fetal distress in pregnant women with COVID-19 have been reported<sup>3</sup>, without clear cause of distress. We describe a placenta with increased perivillous fibrin depositions and chronic and acute intervillitis in a woman with COVID-19. Fibrin depositions and chronic intervillitis may coexist.<sup>7</sup> In the presence of acute intervillitis, however, this has only been described once before, namely in the first described case of proven transplacental transmission of SARS-CoV-2.<sup>6</sup> In that case, maternal thrombocytopenia and prolonged APTT, followed by non-reassuring fetal heart rate and an emergency CD, were noted as well.



<sup>6</sup> A pathologic immune reaction has been proposed as reason for extensive perivillous fibrin depositions and chronic intervillitis, whilst a relationship with viral infections in pregnancy has only been described sporadically. <sup>8,9</sup> Extensive fibrin depositions are associated with adverse obstetrical outcomes <sup>10</sup> and have also been linked to coagulation disorders <sup>11</sup>, corresponding with the abovementioned case. The acute placental intervillous pathologies and especially the extensive fibrin depositions, possibly causing a non-reassuring fetal heart rate tracing, might be related to maternal illness (Diabetes, COVID-19 and possible DIC). Due to pre-existing diabetes, our patient might have been more susceptible for a more severe course.

Literature on COVID-19 in a non-pregnant population suggest a possible prothrombogenic component associated with COVID-19. <sup>12</sup> Also, COVID-19 can be associated with coagulation disorders (COVID-19 associated coagulation disorder, CAC). It is suggested that this coagulopathy may be distinguished from other coagulopathies by a pre-dominant increase in D-dimer and other fibrinogen degradation products. The features of DIC and CAC may however partly overlap. <sup>13</sup> COVID-19-associated coagulopathy was not a described entity at the time of presentation early in the COVID-19 pandemic.

In non-pregnant COVID-19 patients, it is suggested that fibrin deposition in the pulmonary microvasculature is one of the causes of more severe ARDS in some patients. <sup>14</sup> A similar pathological process caused by COVID-19 might occur in the placenta, leading to COVID-19-associated coagulopathy and a non-reassuring fetal heart rate.

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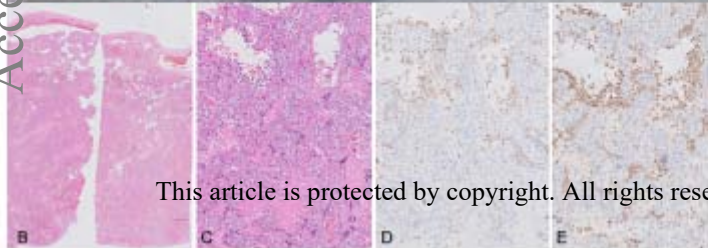
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**Legends for figures and tables.**

Table 1. Laboratory findings during admission

Figure 1. Placental abnormalities of a patient diagnosed with COVID-19.

- (A)** Cross-sections of the placenta with multiple pale areas. Microscopic placental abnormalities of a patient diagnosed with COVID-19.
- (B)** Microscopy overview placenta shows increased perivillous fibrin deposition and intervillitis
- (C)** HE (hematoxylin and eosin stain) detail fibrin around villi and infiltrate.
- (D)** CD68 (Cluster of Differentiation 68) stain to detect histiocytes.
- (E)** Myeloperoxidase (MPX) stain (Granulocytes colour brown) Granulocytes.



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Table 1. Laboratory findings during admission

	<b>Day of admission (ADM)</b>	<b>ADM +1</b>	<b>ADM +2</b>	<b>ADM +3</b>	<b>ADM +4</b>	<b>ADM +5 (delivery)</b>	<b>ADM +5 (postpartum)</b>	<b>ADM + 7 (discharge)</b>
<b>C-reactive protein</b> (<5 mg/L)	49	63	48		14	9.8		
<b>Hemoglobin</b> (7.5-10.0 mmol/L)	5.5	5.8	6.1	6.5	6.2	6.4	4.4	5.7
<b>Hematocrit</b> (0.35-0.45 L/L)	0.29	0.31	0.33	0.35	0.34	0.35	0.23	
<b>MCV</b> (80-100 fL)	77	77	77	77	77	78	77	80
<b>WBC</b> (4.0-10.0 x10 <sup>9</sup> /L)	4.8	3.9	5.1		8.5	9.3	10.3	
<b>Platelets</b> (150-400 x10 <sup>9</sup> /L)	150	131	104	123	118	131	109	170
<b>APTT</b> (25-34 sec)			45	39	38	36	34	35
<b>PT</b> (12.1–15.6 sec)			16.7	16.8	17.4	16.8	17	15.7
<b>Fibrinogen</b> (2.0-4.0 g/L)			1.2	1.0	0.7	0.9	1.7	4.2
<b>D-dimer</b> (<0.50 mg/L)			27	20	9.4		2.6	0.41
<b>Creatinine</b> (49-90 µmol/L)	45	50	46	46	52	50	50	
<b>eGFR</b>	>90	>90	>90	>90	>90	>90	>90	

(>90 ml/m/1.73m <sup>2</sup> )								
<b>Urate</b> (0.12-0.34 mmol/L)	0.18	0.21	0.22	0.22	0.24	0.23	0.25	
<b>Aspartate aminotransferase</b> (<31 U/L)	24	35	37	36	29	32	62	
<b>Alanine aminotransferase</b> (<34 U/L)	9	9	9	8	9	14	17	
<b>Lactate Dehydrogenase</b> (<247 U/L)	220	310	410	460	450	430	360	
<b>Haptoglobin</b> (0.37-2.21 g/L)			1.72					
<b>Protein creatinine ratio (urine)</b> (<30 mg/mmol)	21			<11				
<b>Albumin</b> (35-50 g/L)							28	29
<b>Calcium corrected</b> (2.15-2.55 mmol/L)							2.14	2.39