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Analysis of placental pathology after COVID-19 by timing and severity of infection

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BACKGROUND: COVID-19 during pregnancy can have serious effects on pregnancy outcomes. The placenta acts as an infection barrier to the fetus and may mediate adverse outcomes. Increased frequency of maternal vascular malperfusion has been detected in the placentas of patients with COVID-19 compared with controls, but little is known about how the timing and severity of infection affect placental pathology.

OBJECTIVE: This study aimed to examine the effects of SARS-CoV-2 infection on placental pathology, specifically whether the timing and severity of COVID-19 affect pathologic findings and associations with perinatal outcomes.

STUDY DESIGN: This was a descriptive retrospective cohort study of pregnant people diagnosed with COVID-19 who delivered between April 2020 and September 2021 at 3 university hospitals. Demographic, placental, delivery, and neonatal outcomes were collected through medical record review. The timing of SARS-CoV-2 infection was noted, and the severity of COVID-19 was categorized on the basis of the National Institutes of Health guidelines. The placentas of all patients with positive nasopharyngeal reverse transcription-polymerase chain reaction COVID-19 testing were sent for gross and microscopic histopathologic examinations at the time of delivery. Nonblinded pathologists categorized histopathologic lesions according to the Amsterdam criteria. Univariate linear regression and chi-square analyses were used to assess how the timing and severity of SARS-CoV-2 infection affected placental pathologic findings.

RESULTS: This study included 131 pregnant patients and 138 placentas, with most patients delivered at the University of California, Los Angeles (n=65), followed by the University of California, San Francisco (n=38) and Zuckerberg San Francisco General Hospital (n=28). Most patients were diagnosed with COVID-19 in the third trimester of pregnancy (69%), and most infections were mild (60%). There was no specific placental pathologic feature based on the timing or severity of COVID-19. There was a higher frequency of placental features associated with response to infection in the placentas from infections before 20 weeks of gestation than that from infections after 20 weeks of gestation (P=.001). There was no difference in maternal vascular malperfusion by the timing of infection; however, features of severe maternal vascular malperfusion were only found in the placentas of patients with SARS-CoV-2 infection in the second and third trimesters of pregnancy, not in the placentas of patients with COVID-19 in the first trimester of pregnancy.

CONCLUSION: Placentas from patients with COVID-19 showed no specific pathologic feature, regardless of the timing or severity of the disease. There was a higher proportion of placentas from patients with COVID-19—positive tests in earlier gestations with evidence of placental infection—associated features. Future studies should focus on understanding how these placental features in SARS-CoV-2 infections go on to affect pregnancy outcomes.

Key words: gestational age, maternal vascular malperfusion, obstetrics, pathology, perinatal outcomes, placenta, pregnancy, SARS-CoV-2, umbilical cord

Introduction

Pregnant people are at increased risk of severe COVID-19.[1,2] Evidence suggests that pregnancies complicated by COVID-19 have higher rates of miscarriage, preterm birth, preeclampsia, and preterm premature rupture of membranes.[3] The placenta, which acts as an infection barrier to the fetus, may be uniquely affected in pregnancies complicated by COVID-19, resulting in the observed poorer birth outcomes as many viral infections in pregnancy are associated with specific placental findings on histopathologic examination.[4–6]

Several case reports have demonstrated placental invasion and damage in pregnancies complicated by SARS-CoV-2 infection on histologic evaluation.[7] It is estimated that up to 7% to 21% of placentas show evidence of SARS-CoV-2 invasion, primarily localized to syncytiotrophoblasts.[3,8,9] Placental infiltration of immunologic cells, mostly monocytes and neutrophils, is frequently seen.[3,9,10] Chronic histiocytic intervillositis is rare, but it may be a risk factor for transplacental transmission of SARS-CoV-2.[11,12] Even in the absence of direct viral infection of placental tissue, maternal systemic infection may affect placental development and function and, thus,

pregnancy outcomes. Although no pathognomonic histological pattern exists, higher frequencies of maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), and chronic inflammatory pathologies have been detected across studies.[7,13–15] Unfortunately, these studies are limited by small sample sizes, and most COVID-19 infections occur in the third trimester of pregnancy. A recent study, with a much larger sample size of 870 placentas, found an increased frequency of MVM, including decidual arteriopathy, with increasing frequency seen in more severe COVID-19 infections, compared with controls.[16]

This study aimed to examine the effects of COVID-19 on placental pathology, specifically how the timing and severity of SARS-CoV-2 infection affect pathologic findings. In addition,

AJOG MFM at a Glance
Why was this study conducted? This study aimed to assess how the timing and severity of COVID-19 affect placental pathologic findings.
Key findings There was no specific placental pathologic feature based on the timing or severity of SARS-CoV-2 infection. There was a higher frequency of placental features associated with response to infection from COVID-19 before 20 weeks of gestation than that from COVID-19 after 20 weeks of gestation (*P*=.001). There was no difference in maternal vascular malperfusion (MVM) by the timing of infection; however, severe MVM features were only found in the placentas of patients with COVID-19 in the second and third trimesters of pregnancy.
What does this add to what is known? Our study reports on a larger sample of placentas from patients with SARS-CoV-2 infection, including earlier and milder infections.

the associations with perinatal outcomes were investigated.

Materials and Methods

We conducted a descriptive retrospective cohort study of pregnant people diagnosed with SARS-CoV-2 infection who delivered between April 2020 and September 2021 at the University of California San Francisco (UCSF) Birth Center, the Zuckerberg San Francisco General Hospital Family Birth Center (ZSFG), and the University of California, Los Angeles (UCLA). This study was approved by the institutional review boards (UCSF IRB# 21-33621 [UCSF and ZSFG] and UCLA IRB# 20-000579). Participants were all delivered at these institutions with a confirmed diagnosis of COVID-19 by nasopharyngeal reverse transcription-polymerase chain reaction (PCR) testing during pregnancy, and their placentas were sent for pathology evaluation. We excluded patients who underwent abortions or surgical management for early miscarriages. Patients received COVID-19 PCR testing for either suspected infection because of symptoms or high-risk exposure or routine screening on admission to the hospital.

Demographic and clinical data
We performed medical record reviews using electronic medical records to obtain relevant demographic, placental, delivery, and neonatal outcomes. Baseline demographic information included maternal age, race, and ethnicity. Clinical information included gravidity, parity, body mass index (BMI), maternal comorbidities (chronic hypertension, preeclampsia, pregestational diabetes mellitus, gestational diabetes mellitus, asthma, chronic kidney disease, substance use, in vitro fertilization pregnancies, and other preexisting conditions), use of anticoagulants in pregnancy, fetal and pregnancy complications (multiple pregnancies, fetal growth restriction, clinical chorioamnionitis, placental abruption, and umbilical cord or placental anomalies), and COVID-19 information (severity, gestational age of infection, and trimester of infection). We categorized COVID-19 severity as asymptomatic, mild, moderate, severe, or critical based on National Institutes of Health guidelines.[17] We defined composite maternal morbidity based on the Centers for Disease Control and Prevention criteria[18] and distinguished whether the outcome occurred at the time of delivery or at the time of COVID-19−related admission (Supplemental Table 1). We defined composite neonatal morbidity per Maternal-Fetal Medicine Units Network criteria (Supplemental Table 1).[19]

Placental collection and processing
The placentas of all patients with positive COVID-19 testing were sent for gross and microscopic histopathologic examination at the time of delivery. Histologic examination was performed by subspecialty pathologists who were aware of the patient's COVID-19 status. Photographs of any gross abnormalities on the maternal or fetal surface were taken, the placentas were measured, and trimmed weights were recorded. All placentas were fixed in 10% buffered formalin. Sections submitted included 2 sections of the umbilical cord, 2 sections of membrane, 3 full-thickness sections of the grossly normal-appearing placenta from the chorionic plate to the basal plate, and additional submitted sections of any grossly abnormal placenta. The sections underwent routine processing, were paraffin embedded, sectioned at 3 to 5 μm, and stained with hematoxylin and eosin. The pathologists categorized the pathologic lesions according to the Amsterdam criteria.[20] Placental pathologic findings of interest included placental weight, cord insertion, coiling index, and any evidence of FVM, MVM, placental hypoxia, placental features associated with response to infection, or placental inflammation (Supplemental Table 2). We categorized MVM as none (0 feature), mild (1−2 features), or severe (≥3 features).

Statistical analysis
We collected and managed data using REDCap electronic data capture tools hosted at UCSF.[21,22] We reported demographic and clinical data with mean or median for continuous variables and as frequencies or percentages for categorical variables. We used univariate linear regression and chi-square analyses to assess how the timing and severity of SARS-CoV-2 infection affected placental pathologic findings. We controlled for gestational age in our regression analysis, using both COVID-19 and gestational age as covariates. To investigate the effect of COVID-19 on placental development, we conducted a subgroup analysis of placental infection before and after 20 weeks of gestation, as placentation is usually complete by 20 to 24 weeks of gestation. Data analysis was performed with Stata (version 15; StataCorp, College Station, TX). A *P* value of <.01 was considered significant.

Results

Overall, 131 pregnant patients and 138 placentas were included in this study. Patients were delivered at UCLA (n=65), UCSF (n=38), and ZSFG (n=28). Moreover, 40% of participants identified as "other" for race and ethnicity, and 53% of participants identified as "not Hispanic or Latino." The most common maternal comorbidities included BMI of >30 kg/ m^2 (n=55 [50%]), gestational hypertension (n=21 [16%]), asthma (n=20 [15%]), and gestational diabetes mellitus (n=20 [15%]). For fetal characteristics, 10% of patients had fetal growth restriction, and 9% of patients had a diagnosis of clinical chorioamnionitis. Most patients were diagnosed with COVID-19 in the third trimester of pregnancy (69%), followed by the second trimester of pregnancy (24%) and the first trimester of pregnancy (8%). Most SARS-CoV-2 infections were mild (60%). Approximately half of the patients met one or more criteria for the composite maternal morbidity at the time of a COVID-19 —related admission, compared with approximately a fifth of patients meeting one or more criteria at the time of delivery. The participant demographic details are shown in Table 1.

Most infants were born at term (median gestational age, 38.6 weeks; interquartile range [IQR], 36.7—39.3) by vaginal delivery (59%). Moreover, 27% of neonates were born preterm, and 8% of neonates were small for gestational age. In addition, 35% of neonates required neonatal intensive care unit (NICU) admission, and 37% of neonates met one or more criteria for composite neonatal morbidity, despite high median Apgar scores (8 at 1 minute and 9 and 5 minutes). The most common reason for NICU admission was prematurity. The most common components of the composite severe neonatal morbidity were NICU admission (n=46 [35%]), continuous positive airway pressure or supplemental oxygen (n=29 [21%]), and respiratory distress syndrome (n=24 [18%]). The delivery and neonatal outcomes are shown in Table 2.

Evaluation of placental pathologic findings by trimester of SARS-CoV-2 infection (Table 3) revealed no

TABLE 1
Participant demographic characteristics

Characteristic	Total N	Values
Maternal age (y), mean (SD)	131	31.2 (6.6)
Gravidity, median (IQR)	131	2 (1—3)
Parity, median (IQR)	131	1 (0—2)
BMI (kg/m^2), mean (SD)	109	31.3 (7.4)
Race, n (%)	131	
Other		52 (39.7)
White		25 (19.1)
Unknown or not reported		25 (19.1)
Asian		18 (13.7)
Black		11 (8.4)
>1 race		0 (0)
Ethnicity, n (%)	131	
Hispanic or Latino		58 (44.3)
Not Hispanic or Latino		69 (52.7)
Unknown or not reported		4 (3.1)
Maternal comorbidities, n (%)		
Chronic hypertension	131	8 (6.1)
Gestational hypertension	131	21 (16.0)
Preeclampsia without severe features	131	7 (5.3)
Preeclampsia with severe features	131	15 (11.5)
Pregestational diabetes mellitus	131	2 (1.5)
Gestational diabetes mellitus	131	20 (15.3)
BMI>30 kg/m^2	131	55 (49.6)
Asthma	111	20 (15.3)
Other preexisting pulmonary condition[a]	131	4 (3.1)
Chronic kidney disease	131	1 (0.8)
Substance use	130	3 (2.3)
IVF pregnancy	131	7 (5.3)
Anticoagulation in antepartum period, n (%)	67	
Aspirin		18 (26.9)
Lovenox		2 (3.0)
Both		2 (3.0)
None		45 (67.2)
Abnormal genetic screening, n (%)	131	10 (7.6)
Fetal and pregnancy complications, n (%)	131	
Multiple pregnancy		8 (6.1)
Fetal growth restriction		13 (9.9)
Clinical chorioamnionitis		12 (9.2)
Placental abruption		2 (1.5)

(continued)

TABLE 1
Participant demographic characteristics *(continued)*

Characteristic	Total N	Values
Umbilical cord or placental anomalies[b]		5 (3.8)
Trimester when COVID-19 was diagnosed, n (%)	131	
First		10 (7.6)
Second		31 (23.7)
Third		90 (68.7)
COVID-19 severity, n (%)	131	
Asymptomatic		30 (22.9)
Mild		78 (59.5)
Moderate		10 (7.6)
Severe		4 (3.1)
Critical		9 (6.9)
Interval between date of COVID-19 diagnosis and due date (d), median (IQR)	129	54 (20−112)
Interval between first COVID-19 symptoms and due date (d), median (IQR)	80	72 (39−129)
Composite maternal morbidity, n (%)[c]	131	
At the time of delivery		28 (21.2)
At the time of COVID-19 related admission		71 (53.8)

BMI, body mass index; *IQR*, interquartile range; *IVF*, in vitro fertilization; *SD*, standard deviation.

[a] Included history of pulmonary embolism (n=1), sleep apnea (n=1), Hodgkin lymphoma (n=1), and latent tuberculosis (n=1); [b] Included single umbilical artery (n=1), velamentous cord insertion, marginal cord insertion (n=1), vasa previa, placenta previa (n=1), and placenta accreta (n=1); [c] Refer to Supplemental Table 1 for more details

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significant association among FVM, MVM, placental hypoxia, placental response to infection, and placental inflammation and trimester of infection (P>.04). Interestingly, there was an association between placental response to infection and timing of SARS-CoV-2 infection when using 20 weeks of gestation as a timing cutoff, with a higher frequency of placental features associated with infection seen in pregnancies complicated by infection before 20 weeks of gestation than in pregnancies complicated by infection at >20 weeks of gestation (11/19 [58%] vs 27/118 [23%], respectively; P=.001) (Table 5).

There was no difference in features of MVM; however, severe features were only found in infections in the second and third trimesters of pregnancy and not infections in the first trimester of pregnancy. Placental weight was greatly associated with severity of SARS-CoV-2 infection (P=.0005), with smaller placentas found in more severe or critical infections (Table 4), but this finding did not hold when controlling for gestational age (P=.03). There was a higher proportion of hypercoiled umbilical cords in asymptomatic infections than in mild, moderate and severe, or critical

TABLE 2
Delivery and neonatal outcomes

Characteristic	Total N	Values
Gestational age at delivery (wk), median (IQR)	131	38.6 (37.0−39.0)
Mode of delivery, n (%)	131	
Vaginal (including operative)		77 (59.0)
Cesarean		54 (41.0)
Preterm delivery (<37 wk), n (%)	131	35 (27.0)
Estimated or quantitative blood loss (mL), mean (SD)	131	637 (79)
Required blood transfusion, n (%)	131	7 (5.3)
Birthweight (g), mean (SD)	135	2916 (860)
Small for gestational age, n (%)	136	11 (8.0)
Infant sex, n (%)	137	
Male		71 (52.0)
Female		66 (48.0)
Apgar score (1-min), median (IQR)	137	8 (7−8)

(continued)

TABLE 2
Delivery and neonatal outcomes *(continued)*

Characteristic	Total N	Values
Apgar score (5-min), median (IQR)	137	9 (8−9)
NICU admission, n (%)	135	47 (35.0)
Composite neonatal morbidity, n (%)[a]	139	51 (37.0)

IQR, interquartile range; *NICU*, neonatal intensive care unit; *SD*, standard deviation.

[a] Refer to Supplemental Table 1 for more details

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infections (P=.01). Most placentas demonstrated at least 1 pathologic feature. Only 1 of 19 placentas from patients with COVID-19 at <20 weeks of gestation (5%) and 31 of 118 placentas from patients with SARS-CoV-2 infection at >20 weeks of gestation (26%) had no placental lesion. We noted 1 placenta that met the criteria for SARS-CoV-2 placentitis based on the triad of histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis.[23] The patient who delivered this placenta was diagnosed with a mild COVID-19 in the third trimester of pregnancy.

Comment
Principal findings
In this retrospective study of 131 pregnant patients with SARS-CoV-2 infection from 3 California hospitals, we found no specific placental pathologic features based on the timing or severity of infection. Placental features associated with

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TABLE 3
Placental pathologic findings by timing of COVID-19

Variable	n	Total	First trimester (n=11)	Second trimester (n=35)	Third trimester (n=92)	P value
Placental weight (g), mean (SD)	137	422 (130)	391 (158)	383 (133)	440 (122)	.06
Placental weight of <10th percentile	134	21 (16)	4 (36)	4 (12)	13 (14)	.14
Cord insertion	135					.64
Central		28 (21)	3 (27)	5 (15)	20 (22)	
Eccentric		101 (75)	8 (73)	28 (85)	65 (71)	
Marginal		4 (3)	0 (0)	0 (0)	4 (4)	
Velamentous		2 (2)	0 (0)	0 (0)	2 (2)	
Hypercoil	138	36 (26)	0 (0)	9 (26)	27 (29)	.11
Hypocoil	138	2 (2)	0 (0)	1 (3)	1 (1)	.69
Fetal vascular malperfusion: any feature	138	16 (12)	2 (18)	5 (14)	9 (10)	.60
Maternal vascular malperfusion	138					.44
None		88 (64)	6 (55)	19 (54)	63 (69)	
Mild		46 (33)	5 (46)	14 (40)	27 (29)	
Severe		4 (3)	0 (0)	2 (6)	2 (2)	
Any feature		50 (36)	5 (46)	16 (46)	29 (32)	.27
Evidence of placental hypoxia: any feature	138	40 (29)	4 (36)	7 (20)	29 (32)	.38
Evidence of placental response to infection: any feature	138	38 (28)	5 (46)	14 (40)	19 (21)	.04
Evidence of placental inflammation: any feature	138	21 (15)	1 (9)	6 (17)	14 (15)	.81
No placental lesion	138	32 (23)	1 (9)	8 (23)	23 (25)	.50

Data are presented as number (percentage), unless otherwise indicated. Complete lists of features for each category are listed in Supplemental Tables 2 and 3.

SD, standard deviation.

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TABLE 4
Placental pathologic findings by severity of COVID-19

Variable	n	Total	Asymptomatic (n=31)	Mild or moderate (n=93)	Severe or critical (n=14)	P value
Placental weight (g), mean (SD)	137	422 (130)	455 (141)	429 (117)	299 (127)	.0005[a]
Placental weight of <10th percentile	134	21 (16)	6 (19)	13 (14)	2 (15)	.81
Cord insertion	135					.50
Central		28 (21)	4 (13)	22 (24)	2 (17)	
Eccentric		101 (75)	27 (87)	65 (71)	9 (75)	
Marginal		4 (3)	0 (0)	3 (3)	1 (8)	
Velamentous		2 (2)	0 (0)	2 (2)	0 (0)	
Hypercoil	138	36 (26)	14 (45)	21 (23)	1 (7)	.01
Hypocoil	138	2 (2)	0 (0)	2 (2)	0 (0)	.61
Fetal vascular malperfusion: any feature	138	16 (12)	3 (10)	12 (13)	1 (7)	.76
Maternal vascular malperfusion	138					.55
None		88 (64)	22 (71)	59 (63)	7 (50)	
Mild		46 (33)	9 (29)	31 (33)	6 (43)	
Severe		4 (3)	0 (0)	3 (3)	1 (7)	
Any feature		50 (36)	9 (29)	34 (37)	7 (50)	.40
Evidence of placental hypoxia: any feature	138	40 (29)	10 (32)	27 (29)	3 (21)	.76
Evidence of placental response to infection: any feature	138	38 (28)	7 (23)	30 (32)	1 (7)	.11
Evidence of placental inflammation: any feature	138	21 (15)	4 (13)	15 (16)	2 (14)	.91
No placental lesion	138	32 (23)	7 (23)	21 (23)	4 (29)	.88

Data are presented as number (percentage), unless otherwise indicated. Complete lists of features for each category are listed in Supplemental Tables 2 and 4.

SD, standard deviation.

[a] *P*<.01.

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response to infection were significantly more common when COVID-19 occurred before 20 weeks of gestation. Severe features of MVM were only seen in infections in the second and third trimesters of pregnancy, but there was no statistically significant difference.

Results in the context of what is known

Our findings are consistent with available evidence that has not identified any pathognomonic histologic patterns in human placentas following maternal SARS-CoV-2 infection. To date, published work has been largely on infections in the third trimester of pregnancy.[13] Multiple studies have reported a higher frequency of MVM in the placentas of pregnant patients with SARS-CoV-2 infection, which can have significant clinical sequelae for the pregnancy.[9,24–26] Although 36% of the placentas in our studies demonstrated features of MVM, we did not see differences based on timing or severity of infection.

We found a statistically significant difference in placental response to infection by the timing of infection, with a greater proportion of placentas with these features from maternal infections occurring before 20 weeks of gestation. In a systematic review of placental morphology and histopathologic lesions associated with SARS-CoV-2 infection, 10 studies reported inflammatory changes;[7] however, the overall rates of acute and chronic inflammation were not increased compared to controls.[14] This differing finding may be due to the increased number of infections in the first and second trimesters of pregnancy in our cohort. The persistence of these findings until delivery at term suggests that maternal SARS-CoV-2 infection may cause chronic changes to placental function.

There was a higher proportion of hypercoiled umbilical cords in asymptomatic patients with SARS-CoV-2 infections. Factors that determine umbilical cord coiling are largely unknown, but it is believed that coiling is established early in pregnancy and increases only insignificantly later on in pregnancy.[27] Hypercoiled cords are known to be significantly associated with poor neonatal outcomes.[28,29] Few studies on placental pathology in SARS-CoV-2 infection comment on umbilical cord coiling;[7] thus, the significance is unknown. Our findings of hypercoiled umbilical cords may have contributed to our high rate of NICU admission (35%).

TABLE 5
Placental pathologic findings by timing of COVID-19 (<20 or >20 weeks of gestation)

Variable	n	Total	<20 wk (n=19)	>20 wk (n=118)	*P* value
Placental weight (g), mean (SD)	137	422 (130)	428 (34)	421 (12)	.42
Placental weight of <10th percentile	134	21 (16)	5 (28)	16 (14)	.13
Cord insertion	135				.79
Central		28 (21)	4 (21)	24 (21)	
Eccentric		101 (75)	15 (79)	86 (74)	
Marginal		4 (3)	0 (0)	4 (4)	
Velamentous		2 (2)	0 (0)	2 (2)	
Hypercoil	138	36 (26)	1 (5)	35 (30)	.03
Hypocoil	138	2 (2)	0 (0)	2 (2)	.57
Fetal vascular malperfusion: any feature	138	16 (12)	4 (21)	12 (10)	.17
Maternal vascular malperfusion	138				.27
None		88 (64)	9 (47)	79 (66)	
Mild		46 (33)	9 (47)	37 (31)	
Severe		4 (3)	1 (5)	3 (3)	
Any feature		50 (36)	10 (53)	40 (34)	.11
Evidence of placental hypoxia: any feature	138	40 (29)	8 (47)	32 (27)	.18
Evidence of placental response to infection: any feature	138	38 (28)	11 (58)	27 (23)	.001[a]
Evidence of placental inflammation: any feature	138	21 (15)	3 (16)	18 (15)	.94
No placental lesion	138	32 (23)	1 (5)	31 (26)	.05

Data are presented as number (percentage), unless otherwise indicated. Complete lists of features for each category are listed in Supplemental Table 2.

SD, standard deviation.

[a] *P*<.01.

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Clinical and research implications
This study adds to the growing body of evidence on the effects of SARS-CoV-2 infection on the placenta. Specifically, this is one of the larger cohorts published to date and includes earlier and milder infections, as most studies have focused on infections in the third trimester of pregnancy and/or case series with more severe outcomes.[30] Future studies should include patients with SARS-CoV-2 infection earlier in pregnancy and those with milder infections. Furthermore, the link between placental pathology findings in COVID-19 and obstetrical and/or neonatal outcomes is poorly understood. An improved understanding of these associations is paramount to assist in potential perinatal interventions, such as increased monitoring of the pregnancy through antenatal testing and ultrasonography.

Strengths and limitations
There are several limitations to this study. First, we did not use a COVID-19–negative control group for comparison. As it is challenging to find an appropriate control group to compare placental findings (as placentas from "normal" pregnancies do not undergo placental pathologic evaluation), we opted to compare pathologic features based on the timing and severity of infection. Second, we did not have molecular testing (PCR or immunohistochemistry) testing for SARS-CoV-2 in placental tissue; however, molecular detection of SARS-CoV-2 in the placenta is rare, and all patients had confirmation of SARS-CoV-2 infection by nasopharyngeal PCR. Third, although we had a relatively small cohort of patients and placentas, the current study is one of the largest published to date. Lastly, we are unable to directly determine the causality between SARS-CoV-2 infection and placental findings.

The main strengths of this study are the large sample size, including all cases of COVID-19 across pregnancy trimesters. The bulk of the published literature on SARS-CoV-2 infection is for infections in the third trimester of pregnancy; most studies are case reports or series on severe adverse outcomes. This study was designed to investigate placental pathology based on the timing of SARS-CoV-2 infection during pregnancy. Furthermore, we had consistency in pathologic reporting as a small group of pathologists reviewed most of the placentas.

Conclusions
We report on a large sample of pathologic placental features in pregnant

patients with SARS-CoV-2 infection, across trimesters and severity of infection. There was a higher proportion of earlier infections with evidence of placental infection–associated features. Future studies should focus on understanding how these placental features in SARS-CoV-2 infections go on to affect pregnancy outcomes and whether specific interventions need to be taken during the pregnancy to prevent potential negative consequences. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023.100981.

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